BMC Cancer

SYSTEMATIC REVIEW Open Access

Paediatric acute myeloid leukaemia epidemiology, treatment approaches, and outcomes in africa: A review of the literature

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Abstract

Background Paediatric acute myeloid leukaemia (AML) is a challenging disease in low- and middle-income countries with limited African data. This study reviewed the existing literature regarding paediatric AML in Africa.

Methods A literature search was performed using PubMed, Embase, Google Scholar, Research4Life, and African Journals Online for published studies on paediatric AML in Africa, with keywords acute myeloid leukaemia, children, Africa, and country-specific names for all the African countries. The review included all abstracts and publications from Africa from January 2004 until January 2024, involving children between 0 and 17 years old with outcome data.

Results Of 164 studies identified, 22 were included in the data analysis, with 2230 children included. Treatment regimens varied widely. Complete remission rates ranged between 23.1% and 88.9% (median 55.0%) for AML in general and between 72.6% and 95.0% for acute promyelocytic leukaemia (APL). The results also showed high rates of early deaths (5 – 96%; median 29.3%) and treatment-related mortality rates (11.3 – 47.1%; median 21.0%) among children with AML in the African setting. The five-year probability of event-free survival ranged from 14.8% for high-risk disease to 69.4% for APL. The five-year probability of overall survival ranged between 14% and 31.9% for non-APL (median 29.5%). Treatment abandonment varied between 3% and 50% (median 12.7%). Only 14 patients received a hematopoietic stem cell transplantation.

Conclusion There is limited data regarding paediatric AML and outcomes in Africa, with variable treatment regimens, treatment outcomes, early deaths, treatment-related mortality, and abandonment rates. Adapted treatment protocols adjusted to local settings should be implemented with improved supportive health care.

Keywords Acute myeloid leukaemia, Paediatric, Epidemiology, Outcomes, Africa

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Introduction

Paediatric acute myeloid leukaemia (AML) is a heterogeneous disease of the myeloid precursors in the bone marrow and poses significant management challenges, especially in low- and middle-income countries (LMICs). The disease and management in Africa have limited data. Most AML cases arise as de novo malignancies in previously healthy individuals; there are cases of AML occurring as a secondary malignancy [1, 2]. Paediatric AML accounts for 15–20% of childhood acute leukaemia [3, 4], but the exact incidence and proportion of AML to acute lymphoblastic leukaemia (ALL) is unknown in Africa due to underreporting by cancer registries and potential misdiagnosis in the clinical setting [4, 5]. In the United States, the 2005–2009 estimated incidence of childhood AML was 7.7 cases per one million children aged 0–14 years [6]. A Nigerian study reported that 50% of all acute leukaemia in Africa was AML [7], but the true prevalence and treatment outcomes of paediatric AML in the African context should be established.

The outcomes of AML have greatly improved in high-income countries (HICs), with a five-year overall survival (OS) of up to 74% ± 2% [8, 9] for AML in general. Recent data from the Children's Oncology Group (COG-AAML 1331) study reported a two-year event-free survival (EFS) and OS for acute promyelocytic leukaemia (APL) of 98% and 99%, respectively, for standard-risk diseases [10]. This improved survival is mostly attributed to improved diagnostic techniques, risk stratification, refined treatment strategies, better supportive care measures, and improved salvage therapy, including refining hematopoietic stem cell transplantation (HSCT) [8, 11, 12]. In addition, AML is treated under the umbrella of harmonized cooperative group protocols. AML continues to be a challenging disease to treat in resource-limited settings [13], such as countries in Africa, with notable differences in the treatment outcomes. Of concern is that more than 80% of children with cancer worldwide live in low-income countries (LICs), where the level of care is considerably lower than in HICs [14].

The causes of this great disparity in outcomes in low- and middle-income countries (LMICs) include late presentation, limited infrastructure for accurate diagnosis, lack of risk stratification, inadequate supportive care, lack of cytogenetic risk-based treatment, and high rates of treatment abandonment [15–17]. Likewise, high rates of infectious complications, including bacterial, fungal, and viral infections, pose significant challenges in LMICs [17–20]– compounding on the disparity. In addition, the complexity of quality care for AML is substantial, many of which are not always available in LMICs. Notable is the gross inadequate capacity for supportive care and intensive care facilities to cope with the intensity of treatment and related chemotherapy toxicities that lead to early death [16, 21]. Likewise, high rates of comorbidities, including malnutrition and sepsis, in children presenting with AML in African settings would potentiate the toxicity profile of the current standard of treatment based on high-intensity chemotherapy regimens [22].

Literature on the treatment approaches and outcomes of pediatric AML in the African context is scarce. A previous systematic review in global LMICs suggests great disparities in managing pediatric AML between LMICs with outcomes that are largely inferior [23]. However, only three African countries, two of which are from North Africa and only one from sub-Saharan Africa, were included in the study. In addition, the lack of intra-country, regional, and continental collaborative efforts in cooperative groups and harmonized treatment protocols in the African context hinders a better understanding of the poor outcomes in this context and harnessing strategies to improve survival. This review was conducted with a focus on the available literature with the aim to gain better insight regarding the epidemiology, treatment strategies, and outcomes of pediatric AML in Africa.

Methods

Literature search

This literature review was aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [24] and was not registered. A literature search was performed using PubMed, Embase, Google Scholar, Research4Life, and African Journals Online for published studies on pediatric AML in Africa. The search terms included a combination of acute myeloid leukemia, AML, children, pediatric, Africa, developing countries, low-income countries, and country-specific names as our search terms (Supplementary Table S1). We included only articles in English and published from Africa from January 2004 until January 2024 (20-year period). Children diagnosed with AML were defined as persons between 0 and 17 years of age.

Study selection

The inclusion criteria for studies were (a) studies on pediatric AML in Africa; (b) including patients aged 0–17 years at diagnosis; (c) treating institution in an African country; and (d) including data on the outcome of pediatric AML. We excluded studies with the following criteria: (a) review articles; (b) studies that do not contain any data on outcome; (c) studies published outside the period under consideration; and (d) studies including both children and adults or mixed leukemia subtypes with no disaggregation of data and outcome by age or leukemia subtype at data analysis. Case reports and case series of less than seven cases of pediatric AML were excluded

from this review. The articles were independently screened by two of the authors, and the final determination of eligibility of studies was reached by consensus of all the authors. Conflicts were resolved by a third-party adjudicator.

Data extraction

Data from the included studies were extracted using standardized data collection forms. The data were extracted manually and independently by two reviewers so as to minimise bias and errors in data extraction. The following information was extracted from each study, where they were available: (1) Characteristics of included studies: first author, year of publication, study period, type of study, country of study origin, regional location of the country, World Bank economic status of the country of study, and sample size (i.e., number of patients diagnosed with AML); (2) clinical characteristics of the patients: age at diagnosis, sex; (3) treatment protocol used; (4) availability of hematopoietic stem cell transplant (HSCT); (5) treatment responses: rates of complete remission (CR), early death, treatment-related mortality (TRM), and relapse; (6) probabilities of overall survival (OS) and event-free survival (EFS) or median OS and EFS; (7) treatment abandonment rate; and (8) prognostic factors.

Complete remission rates were calculated from the number of patients who received chemotherapeutic treatment. Early death was defined as death in induction before complete remission is evaluated or achieved, or death within 42 days [17, 25]. Treatment-related mortality was defined as death following any of the cycles of chemotherapy (without evidence of an emerging relapse) [26]. Treatment abandonment was defined as failure to either start or continue treatment with curative intent during four or more consecutive weeks [27, 28].

Statistical analysis

Data from the included studies were extracted, and results were tabulated using Microsoft Word. Descriptive statistics for categorical variables were expressed as frequencies and percentages, while continuous variables were summarised as means with standard deviations where applicable. Statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics Data Editor Version 26).

Assessment of quality

Quality was assessed using the quality assessment tool for observational cohort and cross-sectional studies from the National Heart, Lung, and Blood Institute of the National Institutes of Health [29].

Results

Literature search results and study selection

There were 164 studies identified, of which 38 were duplicates. The remaining 126 articles were assessed, of which 22 met the criteria for inclusion (Fig. 1).

Quality of studies

The quality of included studies was evaluated using an adaptation of the National Heart, Lung, and Blood Institute of the National Institutes of Health's quality assessment tool for observational cohort and cross-sectional studies [30] (Supplementary Table S2). Eleven (50.0%) of the reviewed studies had good overall quality, eight (36.4%) had fair quality, and three (13.6%) had poor quality. Possible sources of reporting bias for the included studies include incomplete outcome analyses, insufficient treatment descriptions, and a lack of data on follow-up rates.

Characteristic of the included studies

Nineteen (86.4%) of the 22 included studies were retrospective single-centre studies [17–20, 31–45], while three (13.6%) were prospective studies [46–48], and only one was a multi-centre study [45]. The studies covered paediatric AML cases diagnosed and treated between 1994 and 2022. Most (86.4%; $n = 19$) were published within the last ten years. By World Bank country income-level classification, 17 (77.3%) countries were lower-middle-income countries, three (13.6%) were low-income countries, and only two (9.1%) were upper-middle-income countries (Table 1).

Geographically, 13 (59.1%) of the studies were from North Africa, and eight (36.4%) were from Sub-Saharan Africa (SSA) countries, including six from Eastern African countries and two from South Africa. Only one (4.5%) of the studies was from West Africa.

Patient characteristics

A total of 2230 children with AML were included in the 22 studies [17–20, 31–48], with the number per study ranging from eight to 687 children with an average of 102 (SD 150) patients per study. Of these, 2,031 (91.1%) received treatment for AML. Eight of the 22 studies included patients with acute promyelocytic leukaemia (APL) [19, 20, 32–34, 40, 42, 45], of which two were dedicated APL studies [42, 45]. Two studies included only children with acute megakaryocytic leukaemia (AMKL) [31, 37]. Various AML subtypes were excluded across the different studies. Two studies in Kenya excluded APL, juvenile myelomonocytic leukaemia (JMML), Down syndrome-associated AML (DS-AML), and myeloid sarcoma, in addition to secondary AML and patients with myelodysplastic syndrome (MDS) in one study [17, 36]. Houssou et al. in Morocco and Semary et al. in Egypt

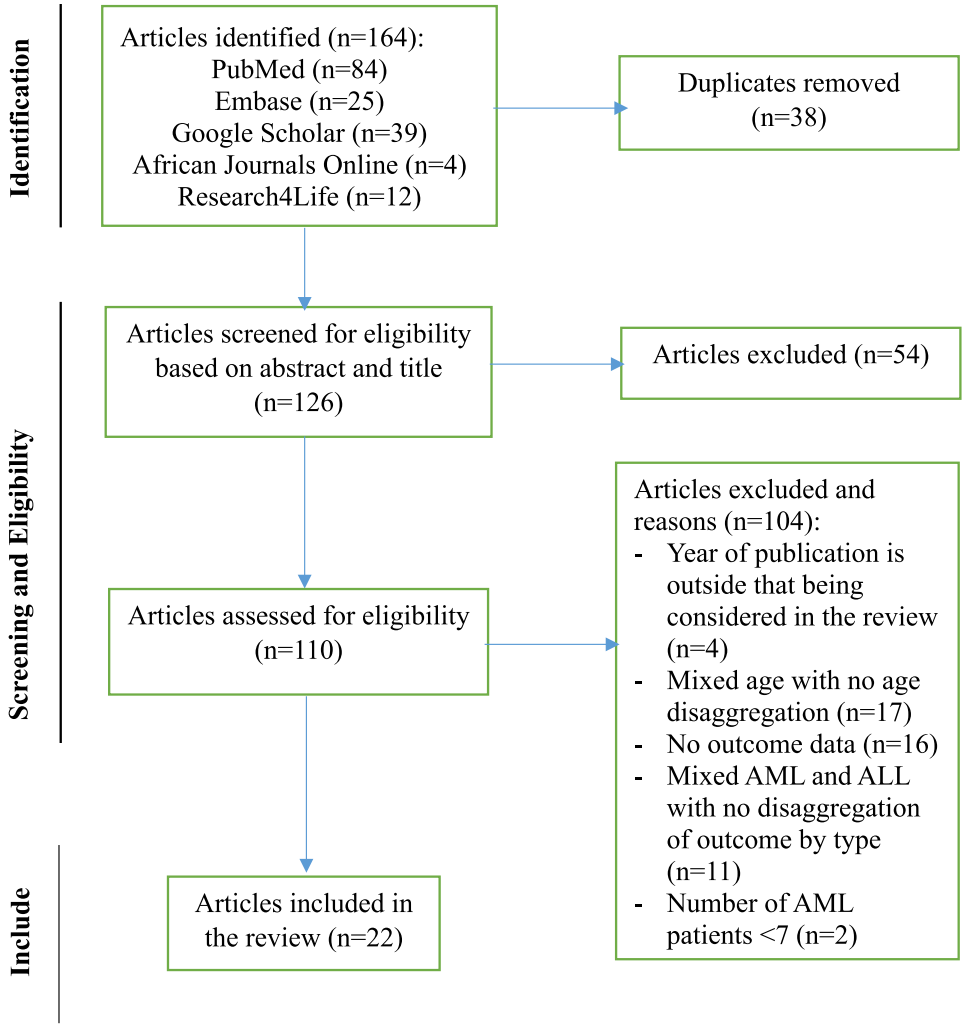


Fig. 1 Algorithm for literature search and the study selection for the literature review

excluded APL, DS-AML, and secondary AML [35, 44], in addition to myeloid sarcoma, in the Egyptian study [35] (see the summary of AML excluded subtypes per study in Table 1).

The age range for the included children was 0–17 years. When the two APL-only studies are excluded, the median age at diagnosis ranged from 1.0 to 11.8 years in 9 studies [18, 20, 31, 35–37, 44, 46, 47] and was much lower (1.0-1.8 years) for patients with AMKL [31, 37]. Seven studies reported mean age, which ranged from 6.1 to 10.8 years per study [17, 19, 32–34, 40, 43]. Overall, the mean and median age was 8 years or more in 52.9% (9/17) of the studies. Males showed a slight predominance across the majority of the studies [17–19, 31–33, 35, 36, 39, 40, 44, 46–48], and sex distribution could not be ascertained in two studies [20, 41]. Overall, 56.3% ($n = 887$) were male and 43.7% ($n = 688$) were female (Table 1).

The age range for the children with APL (FAB M3) as a subtype of AML could only be ascertained from the two studies that included only patients with APL and was 1.4–17.8 years, with a median age at diagnosis of 9.9–12.0 years [42, 45]. Gender-wise, males also showed slight predominance for the two studies combined, with a male-to-female ratio of 1.3:1 [42, 45]. In the six studies that included both non-APL and APL patients, there was no age and sex disaggregation by AML subtype [19, 20, 32–34, 40].

AML treatment protocols

Most of the protocols were adapted from HICs or study cooperative groups, including the Children's Oncology Group (COG), St. Jude Children's Research Hospital, the Berlin-Frankfurt-Münster (BFM) study group, the Medical Research Council (UK MRC) of the United Kingdom, the International Society of Paediatric Oncology—Paediatric Oncology in Developing Countries (SIOP-PODC), Tata Memorial Hospital, and APL-specific protocols. (See Table 2 for a summary of treatment protocols and chemotherapeutic agents used).

Table 1 Pediatric acute myeloid leukaemia (AML) studies and patient characteristics in Africa

Study	Type of Study	Study period	Country	Economic status	Region of Africa	Number of patients	Inclusion of APL	AML subtypes excluded	Age (years)	Sex	
										M (%)	F (%)
van Weelderen et al. (2021) [13]	Retrospective	2010–2018	Kenya	LMIC	East	73	No	APL, JMML, DS-AML, Myeloid sarcoma, secondary AML, MDS	0–16 Mean 8.6	41 (56.2)	32 (43.8)
Leonora de Jager (2022) [34]	Retrospective	1998–2017	South Africa	UMIC	South	119	Yes (23 patients)	DS-AML, Myelodysplasia, Therapy-related AML	0–18 Mean 7.0	53 (44.5)	66 (55.5)
Chellakhi et al. (2015) [46]	Prospective	2011–2014	Morocco	LMIC	North	44	Not stated	None	≤ 15 Median 8.0	19 (54.3)	16 (45.7)
Oyamo and Arega (2023) [19]	Retrospective	2016–2020	Ethiopia	LIC	East	38	Yes	None	0–15 Mean 8.0	21 (55.3)	17 (44.7)
Kersten et al. (2013) [18]	Retrospective	2008–2010	Tanzania	LMIC	East	25	Not stated	None	2–18 Median 9.0	13 (52.0)	12 (48.0)
Houssou et al. (2016) [44]	Retrospective	2011–2015	Morocco	LMIC	North	41	No	DS-AML, APL, Secondary AML	< 15 Median 7.8	22 (53.7)	19 (46.3)
van Weelderen et al. (2023) [36]	Retrospective	2010–2021	Kenya	LMIC	East	187 total 83 period 1 39 period 2	No	APL, JMML, Myeloid sarcoma DS-AML	0–17 Median 8.6	69 (56.6)	53 (43.4)
Semary et al. (2020) [35]	Retrospective	2007–2017	Egypt	LMIC	North	623 total 65 (FLT3-ITD)* 558 (FLT3-WT)^	No	APL, secondary AML, DS-AML, Myeloid sarcoma	1.4–18.5 Median 11.8 0.1–18.8 Median 6.2	31 (47.7) 333 (59.7)	34 (52.3) 225 (40.3)
Hafez et al. (2019) [20]	Retrospective	2011–2013	Egypt	LMIC	North	100	Yes	None	8mo-17 Median 5.0	Not stated	Not stated
Maarouf et al. (2019)	Retrospective	2007–2016	Egypt	LMIC	North	80	No	DS-AMKL, Previous diagnosis of BM failure	0.2–15 Median 1.8	46 (57.5)	34 (42.5)
Kandeel et al. (2021) [47]	Prospective	2017–2019	Egypt	LMIC	North	89	No	APL	3wks-18 Median 8.0	50 (56.2)	39 (43.8)
Jeddi et al. (2011) [45]	Retrospective	-	Tunisia	LMIC	North	20	Yes (20 patients)	None	4–19 Median 12	9 (45.0)	11 (55.0)
Nzamu et al. (2020) [33]	Retrospective	2019–2020	Uganda	LIC	East	23 in total {4 APL 3 DS-AML 16 non-APL/DS}	Yes (4 patients)	None	Mean 6.1	16 (70.0)	7 (30.0)
Mamo et al. (2024) [32]	Retrospective	2016–2022	Ethiopia	LIC	East	92	Yes	None	5–10 Mean 7.0	55 (59.8)	37 (40.2)
Cherkaoui et al. (2014) [37]	Retrospective	2003–2010	Morocco	LMIC	North	8	No	AML other than AMKL	6mo-2 Median 1.0	2 (25.0)	6 (75.0)

Table 1 (continued)

Study	Type of Study	Study period	Country	Economic status	Region of Africa	Number of patients	Inclusion of APL	AML subtypes excluded	Age (years)	Sex	
										M (%)	F (%)
Ndlovu et al. 2023 [38]	Retrospective	1994–2014	South Africa	UMIC	South	61	NS	None	0–15	26 (42.6)	35 (57.4)
Beghdoud et al. 2020 [39]	Retrospective	2016–2018	Algeria	LMIC	North	39	NS	None	1–16	24 (61.5)	15 (38.5)
Ali et al. 2021	Retrospective	2009–2018	Egypt	LMIC	North	64	Yes (8 patients)	None	2-<18 Mean 10.8	42 (65.6)	22 (34.4)
Madney et al. 2019 [41]	Retrospective	2007–2016	Egypt	LMIC	North	344	NS	None	NA	NA	NA
Semary et al. 2024 [42]	Retrospective	2012–2019	Egypt	LMIC	North	62	Yes 62 patients	Non-APL	1.4–17.8 Mean 9.2 Median 9.9	37 (59.7)	25 (40.3)
Marielle et al. 2015 [48]	Prospective	2011–2014	Morocco	LMIC	North	9	No	HR cytogenetics	0–15	7 (77.8)	2 (22.2)
Ongotsoyi et al. 2019 [43]	Retrospective	2011–2017	Cameroon	LMIC	West	25	NS	None	1–5 Mean 8	12 (48)	13 (52)

LIC Low-income country, *LMIC* Lower Middle-income country, *UMIC* Upper Middle-income country, *NS* Not stated, *HR* High-risk, *NA* Not available, FLT3-ITD* with allelic ratio (AR)>0.4; FLT3-WT^ (Including FLT3-ITD with AR≤ 0.4); *APL* Acute promyelocytic leukemia, *JMML* Juvenile myelomonocytic leukemia, *AMKL* Acute megakaryoblastic leukemia, *DS-AML* Down syndrome-associated AML, *MDS* Myelodysplastic syndrome, *DS-AMKL* Down syndrome-associated acute megakaryoblastic leukemia

Prephase chemotherapy

Six (27.3%) of the protocols used pre-phase therapy [34, 36, 37, 44, 46, 48] that consisted of hydroxyurea (HU) (66.6%; $n=4$), etoposide (16.7%; $n=1$), and dual therapy with thioguanine (TG) and cytarabine with or without HU (16.7%; $n=1$), respectively, prior to initiation of the dose-intense chemotherapy. In four of these studies, the indication of pre-phase was only based on a total white cell count (WBC) of more than 50,000/mm^3 [37, 44, 46, 48]. In one study, the indication of pre-phase was based on a total white cell count (WBC) of more than 50,000/mm^3, clinical hyperleukocytosis syndrome, and organomegaly [34]. The Kenyan study used the criteria as per SIOP-PODC guidelines for treatment of AML in children in low-resource settings [36] (Table 2).

Induction chemotherapy regimens

Induction courses were based on a two- or three-drug regimen that comprised cytarabine (100 mg/m^2) and an anthracycline (daunorubicin or doxorubicin 50 mg/m^2), with etoposide as a third drug in twelve regimens [18–20, 31, 32, 34, 35, 40, 44, 46–48] or without etoposide in five regimens [17, 33, 36, 37, 43]. These were administered either as a three- and seven-day (3 + 7) or a three- and ten-day (3 + 10) schedule. In three of the protocols, a cytarabine dose of 200 mg/m^2 was used [37, 40, 43]. In two studies, combination induction regimens included high-dose cytarabine plus mitoxantrone (HAM) [34, 47], and in one study, 6-thioguanine plus etoposide plus prednisolone was used [18]. Another study used cytarabine plus doxorubicin plus 6-thioguanine [43]. In eight studies, different regimens were used for the first and second induction cycles, either as a standard [48] or based on risk stratification, with high-risk (HR) disease receiving a different regimen for the second induction phase than that administered in induction phase one [20, 31, 34, 35, 44, 46, 47]. The APL induction regimen consisted of all-trans-retinoic acid (ATRA) plus doxorubicin plus etoposide in a study by Oyamo et al. in Ethiopia [19], while Jeddi et al. used ATRA plus daunorubicin plus cytarabine in one protocol and ATRA plus idarubicin in another protocol [45]—similar to the study by Semary et al. in Egypt [42] (Table 2).

Information on intrathecal therapy (IT) was available in 14 studies [17, 20, 31, 33–37, 40, 42–44, 46, 48]– six of which used triple therapies comprising methotrexate, hydrocortisone and cytarabine [17, 20, 31, 33, 35, 36]; three used only cytarabine [34, 40, 42]; and the IT regimen was not specified in four of these studies [37, 44, 46, 48]. With regards to response assessment, only three studies used minimal residual disease (MRD) [31, 35, 47]. The mode of drug administration (whether bolus or infusion) could only be ascertained in one study– being by infusion [19], and only three studies explicitly stated

Table 2 Treatment protocols for pediatric AML in Africa

Study	Protocol	Use of Prephase	Pre-phase agents	Indications	Induction	Consolidation	Use of Maintenance	Cytogenetics	HSCT availability
van Weelderen et al. (2021) [Kenya] [13]	Local AML protocol (3 + 7 Ind; 3 + 5 Consol)	No	NA	NA	ADx	EA	No	No	No
Leonora de Jager (2022) [South Africa] [34]	BFM AML 1998	Yes	6-TG Ara-C ± HU	WCC > 50,000 ± Organomegaly CHS	ADE (induction 1) HAM (induction 2)	6-TG + Pred + VCR + Arac-C + Doxo + Cyclo + IT Arac-C	CNS irradiation 6-Thioguanine Cytarabine	Yes	No
Chellakhi et al. (2015) [Morocco] [46]	AML-MA 2011	Yes	HU	WBC ≥ 50,000	AD (induction 1) ADE (induction 2)	HiDAC	No	Yes	No
Oyamo and Arega (2023) [Ethiopia] [19]	Local AML protocol (7 + 3), (10 + 3 + 5), and APML	No	-	-	ADx (28 patients) ADxE {1 patient} ATRA, Doxo, Etop (for APML)	NA	No	No	No
Kersten et al. (2013) [Tanzania] [18]	MRC AML15 Local protocol 7 + 3 Tata memorial	No	-	-	ADE AD 6-TG/Etop/Pred	Arac-C	No	No	No
Houssou et al. (2016) [Morocco] [44]	AML-MA-2011	Yes	HU	WBC ≥ 50,000	AD (induction 1) {10 + 3} ADE (induction 2) {10 + 3 + 5}	HiDAC + Dauno (Consol 1) HiDAC + Dauno + L-aspa (Consol 2)	No	Yes	No
van Weelderen et al. (2023) [Kenya] [36]	Local AML protocol *SIOP PODC*	No Yes	Etop	Per SIOP PODC protocol	ADx– period 1 ADx– period 2	Etop 200/m2 + Arac100/m2 HiDAC	No	No	No
Semary et al. (2020) [Egypt] [35]	AAML 0531-COG (2008–2013) AAML 1031-COG (2014–2017)	No No	-	-	$A_{10}Dx_3E_5$ {ind 1 &2} $A_{10}Dx_3E_5$ {ind 1 &2} for LR $A_{10}Dx_3E_5$ {ind 1} and MA {ind 2} for HR	AE-int1; MA-int2; Capizzi-int3 AE– int1 for LR&HR MA -int2 (LR) or HiDAC/L-ASPA int2 for HR if SCT not available	No	Yes	Yes (for IR & HR)
Hafez et al. (2019) [Egypt] [20]	AML02 St Jude AML0631 for APML	No	-	-	ADE–ind 1; ADE ± GO ind 2	Arac + cladribine or Etop or Mitox– consol1 Arac + L-aspa– consol 2 Arac + Mitox– consol 3	No	NR	No
Maarouf et al. (2019) [Egypt]	St Jude AML02 COG AAML0531 COG AAML1031	No	-	-	ADE ADxE ADxE or MA {ind2 for HR}	AE {int1; MA {int2}; Capizzi {int3} AE {int1; MA {int2}; Capizzi {int3} AE {int1}; MA {int2 for LR} or HSCT {for HR} or Capizzi {for HR if SCT is not feasible}	No	Yes	Yes
Kandeel et al. (2021) [Egypt] [47]	Modified COG AAML1031	No	-	-	ADxE {ind 1 and 2} HAM {ind2 for HR}	HAM for LR HiDAC + L-aspa for HR	No	Yes	Yes
Jeddi et al. (2011) [Tunisia] [45]	APL93 {1998–2004} LPA 99 {since 2004}	No	-	-	ATRA, idarubicin ATRA, Dauno, AraC	Dauno, AraC idarubicin, mitoxantrone	ATRA, 6-MP, MTX ATRA, 6-MP, MTX	NA-only APL	No
Nzamu et al. (2020) [Uganda] [33]	COG AAML1331 - APL Modified reduced intensity regimen– DS-AML and other AML	No	-	-	NA AD (10 + 3)	NA HiDAC	No	No	No

Table 2 (continued)

Study	Protocol	Use of Prephase	Pre-phase agents	Indications	Induction	Consolidation	Use of Maintenance	Cytogenetics	HSCT availability
Mamo et al. (2024) [Ethiopia] [32]	7 + 3 protocol ADE protocol AML palliative APML protocol	No	-	-	AD {7 + 3} ADE	NA	No	No	No
Cherkaoui et al. (2014) [Morocco] [37]	AML-MA 2003	Yes	HU	WBC > 50,000	AD {7 + 3}	HiDAC + L-aspa	No	Yes* not risk stratification	NR
Ndlovu et al. 2023 [South Africa] [38]	NR	No	-	-	NA	NA	-	No	
Beghdoud et al. 2020 [Algeria] [39]	NR	No	-	-	NA	NA	-	No	No
Ali et al. 2021 [Egypt]	Modified AML-BFM Modified MRC AML ATRA-based for APL	No	-	-	ADx ADE ATRA, Idarubicin	Mitox, Cytarabine ATRA, Idarubicin	Ara-C ARTA, 6-MP, MTX	Yes* not risk stratification	NR
Madney et al. 2019 [Egypt] [41]	Local AML protocol– 2007–2010§ Local AML protocol– 2011–2013π Local AML protocol– 2014–2916¥	No	-	-	NA	NA	-	No	NR
Semary et al. 2024 [42] [Egypt]	COG AAML0631	No	-	-	ATRA, Idarubicin +/- Dexamethasone	ATRA, IDA, Mitox– consol 1 ATRA, IDA– consol 2 ATRA, IDA, HiDAC– consol 3	ARTA, 6-MP, MTX	Yes - APML	NR
Marielle et al. 2015 [Morocco] [48]	AML MA 2011	Yes	HU	WBC > 50,000	AD– Induction 1 ADE– induction 2	HiDAC (3 g/m2), Dauno– consol 1 HiDAC (3 g/m2), L-Aspa– consol 2 HiDAC (1 g/m2), Dauno– consol 3		Yes	NR
Ongotsoyi et al. 2019 [Cameroon] [43]	NA	No	-	-	ADx + 6-TG– protocol 1 AD or ADx– protocol 2	Etop, Purinethol– protocol1 AD– consol 1, protocol 2 ADE– consol 2 Ara-C. L-Aspa - consol 3		No	No

Ind Induction, *Concol* Concolidation, *APML* Acute promyelocytic leukaemia; HU, Hydroxyurea, *Etop* Etoposide, *AD* Cytarabine & daunorubicin, *ADE* Cytarabine, daunorubicin & etoposide, *ADxE* Cytarabine, doxorubicin & etoposide, *HAM* High-dose cytarabine & mitoxantrone, *ADx* Cytarabine & doxorubicin, *MA* Mitoxantrone & cytarabine, *Dauno* Daunorubicin, *Doxo* Doxorubicin, *Cyclo* Cyclophosphamide, *IT* Intrathecal, *ATRA* All-transretinoic acid, *HiDAC* High-dose cytarabine, *L-aspa* L-asparaginase, *AE* HiDAC + Etoposide, *6-TG* 6-thioguanine, *Ara-C* Cytarabine arabinoside, *GO* Gemtuzumab ozogamicin, *Pred* Prednisolone, *VCR* Vincristine, *Mitox* Mitoxantrone, *IDA* Idarubicin, *6-MP* 6-Mercatopurine, *MTX* Methotrexate, *WBC* White blood cell, *SIOP PODC* International Society of Paediatric Oncology– Paediatric Oncology in Developing Countries, *CNS* Central nervous system, *Ind 1 &2* Induction 1 and 2, *LR* Low-risk, *IR* Intermediate-risk, *HR* High-risk, *Int* Intensification, *HSCT* Haematopoietic stem cell transplantation, *SCT* Stem cell transplantation, *NA* Not available, *NR* Not reported, §Less intensified induction without antimicrobial prophylaxis; πLess intensified induction with antimicrobial prophylaxis ¥ Intensified induction with antimicrobial prophylaxis; NA, Not available, NR, Not reported

Table 3 Treatment outcomes of children with AML in Africa

Study	Number of patients {Treated}	CR % (*n*)	ED§ % (*n*)	TRM % (*n*)	Total deaths % (*n*)	Abandonment % (*n*)	Relapse % (*n*)	Salvage therapy	pOS (%)	pEFS (%)
van Weelderen et al. (2021) [Kenya] [13]	73 {55}	33.0 {18}	45.5 {25}	NA	NA	22.0 {16/73}	56.0 {10/18}	None	2 year; 7.2 (SE 3.7)	2 year; 3.7 (SE 2.5)
Leonora de Jager (2022) [South Africa] [34]	119 {109}	35.5 {42} (13%¥) 34% SR 28.6% IR 40.7% HR	31.9 {38}	NA	60.6 {84} (69.6¥) 58.0% SR* 57.1% IR* 81.5% HR*	31.1 {37}	24.0 {29}	None	5 year; 31.9 (30.4 APML) 44.0% SR 42.9% IR 22.2% HR	5 year; 24.4 (26.1 APML) 34.0% SR 42.9% IR 14.8% HR
Chellakhi et al. (2015) [Morocco] [46]	44 {35}	62.0 {22} 55 FR 32 IR 33 UR	20.0 {7}	NA	44% overall 11% FR 16% IR 16% UR	11.4 {4}	11.0 overall 22.0 FR 4.0 IR 16.0 UR	None	2 year; 41.2 overall 53.3 FR 34.4 IR 55.6 UR	NA
Oyamo and Arega (2023) [Ethiopia] [19]	38 {33}	66.7 {22}	30.3 {10}	NA		NA	NA	None	NA	NA
Kersten et al. (2013) [Tanzania] [18]	25 {24}	25.0 (6)	96.0 {24}	21.0 (5/24)		4.0 {1}	21.0 {5}	None	NA	1 year; 6.3 (95% CI 0.4–24) 2 year; 0.0 Median 1 month
Houssou et al. (2016) [Morocco] [44]	41 {41}	68.3 {28} 100% FR 70% IR	14.6 {6}	NA	- 0% FR	NA	NA	NA	4 year; 41.9 60.0% FR 35.4% IR 40.0% UF	4 year; 25.1 60.0% FR 34.0% IR 20.0% UF
van Weelderen et al. (2023) [Kenya] [36]	187 {122} total 83 in period 1 39 in period 2	33.3 {21/63} 37.5 (12/32)	46.0 {29/63} 43.8 (14/32)	36.0 {12/33} 47.0 {8/17}		19.0 {16/83} 3.0 {1/39}	57.0 {12/21} 17.0 {2/12}	None	2 year; 10.1 (SE 3.2) 7.5 (SE 3.4) period 1 15.9 (SE 6.1) period 2	2 year; 7.8 (SE 2.7) 4.6 (SE 2.6) period 1 14.7 (SE 5.8) period 2
Semary et al. (2020) [Egypt] [35]	687 {623} 65 FLT3-ITD 558 FLT3-WT	86.7 overall 66.2 {43} FLT3-ITD HAR 89.0 {497} FLT3-WT	23.0 {15} FLT3-ITD 17.2 {30} FLT3-WT	12.3 FLT-ITD 11.3 FLT3-WT	57.5 73.8 {48}- ITD 55.6 {310}-WT	NA	41.9 {18/43} 24.7 {138/558}	Yes CT	3 year; 26.9 FLT3-ITD 62.5 FLT3-WT 77.8 Allo-BMT 16.3 No BMT	3 year; 22.8 FLT-ITD 51.1 FLT-WT 78.8 Allo-BMT 12.8 No BMT
Hafez et al. (2019) [Egypt] [20]	100 {100}	NS	25.0		58%	NA	NA	NA	NA	NA
Maarouf et al. (2019) [Egypt]	80 {80}	71.3 {57} (CR1)	18.8 {15}	18.8 {15}		NA	27.6% {18/65} ¥30.5 ± 16.1% MRD < 0.1% ¥46.1 ± 22.1% MRD > 0.1%	Yes HSCT	2 year; 52.6 ± 12.3 55%±17% MRD < 0.1% 49.7%±21.3% MRD > 0.1%	2 year; 45.2 ± 12.3 49.2%±17.1% MRD < 0.1% 37.2%±20.5% MRD > 0.1%

Table 3 (continued)

Study	Number of patients {Treated}	CR % (*n*)	ED§ % (*n*)	TRM % (*n*)	Total deaths % (*n*)	Abandonment % (*n*)	Relapse % (*n*)	Salvage therapy	pOS (%)	pEFS (%)
Kandeel et al. (2021) [Egypt] [47]	89 {89}	51.7 {46}		NA		NA	10.1 {9}	Yes SCT	1 year; 26.0 Median 2.6 mo {0.63–19.4}	6 mo; 91.4 (DFS)
Jeddi et al. (2011) [Tunisia]	20 {20}	95.0 {19}	5.0 {1}	NA		NA	10 {2}	Yes CT	4 year; 75.0	4 year; 75.0
Nzamu et al. (2020) [Uganda] [33]	23 {23} overall 16 non-APL/ non-DS 4 APL 3 DS-AML	56.0 {9} non-APL/ non-DS 50.0 {2} APL 33.0 {1}DS-AML		12.5 Non-APL/ DS 25.0 APL 33.0 DS-AML		NA	NA	NA	1 year; 78.6 (95% CI 57.1–100) Non-APML/DS 1 year; 75.0 (95% CI 32.5–100) APML	NA
Mamo et al. (2024) [Ethiopia] [32]	92 {71}	64.2 {36}	29.3 {27}	NA		12.7	10.1	None	1 year; 28.2 3 year; 23.0 Median 4.0 months (2.1–5.9)	1 year; 16.10 Median 1 month (0.8–1.2)
Cherkaoui et al. (2014) [Morocco] [37]	8 {7}	43.0 {3/7}	37.5 {3}	NA	75 {6}	12.5 {1}	28.6 {2}	None	5 year; 14	NA
Ndlovu et al. 2023 [South Africa] [38]	61 {61}	NA	NA	NA	NA	NA	NA	NA	5 year; 29.5 (18.5–42.6)	NA
Beghdoud et al. 2020 [Algeria] [39]	39 {39}	23.1 {9}	NA	NA	38.5 {15}	NA	NA	NA	NA	NA
Ali et al. 2021 [Egypt]	64 {64}	67.5 {23} 57 {12}	18.7 {12} - overall 22.8 {8} 19 {4}	NA	51.5 {33}	NA	23.5 {12}-overall 22 {6} 35.3 {6}	None	3 year; 36.4 ± 5.5	3 year; 35.6 ± 3.5 (DFS) Median: 28.9 months
Madney et al. 2019 [Egypt] [41]	344 {344} 103– period 1 136– period 2 105– period 3	55 {57}–period1 75 {102}-period2 48 {50}-period3	11 {11} 8 {11} 44 {46}	NA NA NA	61 {63} 63 {86} 80 {88}	NA	40 {41}- 16 {22} 6 {6}	None None None	2 year; 30 - period 1 3 year; 37– period 2 2 year; 24– period 3	2 year; 27 (DFS) 3 year; 34 (DFS) 2 year; 34 (DFS)
Semary et al. 2024 [Egypt] [42]	62 {62}	NA	NA	NA	27.4 {17}	NA	NA	NA	5 year; 72.5	5 year; 69.4
Marielle et al. 2015 [Morocco] [48]	9 {9}	88.9 {8}	NA	NA	11.1 {1}	NA	NA	NA	NA	NA
Ongotsoyi et al. 2019 [Cameroon] [43]	25 {20}	45 {9}	NA	NA	70 {14}	50 {10}	NA	NA	1 year; 0 {0} Median: 8.5 months	NA

¥ 2-year cumulative incidence of relapse; §Includes induction death; *CT* Chemotherapy; *Case fatality rate; *CR* Complete remission, *ED* Early death, *TRM* Treatment-related mortality, *pOS* probability of overall survival, *pEFS* probability of event-free survival, *DFS* Disease-free survival, *LR* Low-risk, *FR* Favorable-risk, *SR* Standard-risk, *IR* Intermediate-risk, *HR* High-risk, *UR* Unfavorable risk, *HSCT* Hematopoietic stem cell transplantation, *APML* Acute promyelocytic leukemia, *MRD* Minimal residual disease, *BMT* Bone marrow transplant, *NA* Not available, *SE* Standard error

where medication was administered from– an inpatient setting [18, 20, 40]. Antimicrobial prophylaxis was a practice explicitly stated in ten of the studies– and commonly comprised an antibacterial (sulfamethoxazole/trimethoprim plus or minus ciprofloxacin) and antifungal (fluconazole or ketoconazole or voriconazole or itraconazole) [17–20, 33, 34, 36, 41, 44, 48]. One of these studies also included an antiviral [19].

Consolidation chemotherapy

Consolidation regimens varied among the studies and countries and ranged from a one-drug regimen to combination regimens comprising two to four drugs. Cytarabine, often as high-dose cytarabine (HiDAC), was the most used single-drug chemotherapeutic regimen for consolidation [18, 33, 36, 44, 46, 48]. Combination consolidation regimens were used in several of the studies, commonly comprising cytarabine administered in combination with other agents, including an anthracycline, mitoxantrone, L-asparaginase, and etoposide, among others [17, 20, 31, 34–37, 40, 43–45, 47, 48]. Etoposide was an added drug in consolidation regimens in four studies [17, 20, 31, 36, 43]. Intensification of consolidation was used in three protocols [31, 34, 47], and only two studies used maintenance therapy for non-APL AML that consisted of central nervous system (CNS) irradiation, 6-thioguanine, and cytarabine in one study [34] and three-monthly cytarabine in another study [40]. Haematopoietic stem cell transplantation (HSCT) was an available treatment option in only three Egyptian studies [31, 35, 47]. In one Moroccan study, one patient received HSCT in another country [37]. Fourteen patients underwent HSCT for indications that included unfavourable cytogenetics, minimal residual disease after induction phase one, high-risk disease, and relapsed/refractory disease after achieving morphological CR (Table 2).

Cytogenetic characteristics

Cytogenetic studies were available from ten studies in North Africa, six of which risk-stratified the patients based on cytogenetics. Of these, 293 patients had favourable risk, 413 were intermediate risk, and 198 were unfavourable or had high-risk cytogenetic features. Only one study reported outcomes by individual cytogenetic abnormalities, while another reported specific cytogenetics in eight patients with AMKL [31, 34, 35, 37, 44, 46, 47] (Table 2). Two studies reported cytogenetics, but only for patients with APL [33, 42].

Treatment outcomes of paediatric AML in Africa

Complete remission (CR)

The complete remission (CR) rate was available from all but two [20, 38] of the studies and ranged from 23.1 to 88.9% overall (median 55.5; IQR 37.0-67.7%) when the APL-only studies are excluded, with great variation according to risk stratification (Table 3). CR was over 60% in eight studies [19, 31, 32, 35, 40, 44, 46, 48], while five studies described CR rates of under 40% [17, 18, 34, 36, 39]. Post-induction CR rates ranged from 34 to 100% for favourable-risk AML [34, 44, 46, 48], 28.6–70% for intermediate-risk [34, 44, 46], and 33–40.7% for unfavourable-risk AML [34, 46]. Overall, the mean CR rates in studies with and without etoposide-based induction regimens, excluding the APL-only studies, were 61.6% ± 19.2% and 48.5% ± 18.5%, respectively, but the difference was not statistically significant ($p = 0.112$).

Treatment-related events

The specific treatment-related events in nine of the studies were predominantly sepsis or infectious complications [17, 18, 20, 32–34, 36, 39, 41, 44, 48], followed by haemorrhage [17, 18, 20, 36, 39, 40, 44, 45, 48], respiratory failure [17, 18, 33, 36, 48], other organ failure [18, 20, 40], tumour lysis syndrome [32], electrolyte imbalance [18], typhlitis [32, 40], and mucositis [40].

Induction mortality and treatment-related mortality

Induction mortality and early deaths (ED) were available in 15 studies and ranged from 8.0 to 96% (median 29.3%) [17–20, 31, 32, 34–37, 40, 41, 44, 46]. Five (33.3%) of these studies reported a very high (more than 20%) ED rate with very low (less than 50%) CR rates [17, 18, 34, 36, 37]. Five studies reported TRM that ranged from 11.3 to 47.0% [18, 31, 33, 35, 36], with the lowest TRM rate (11.3%) reported among patients with FLT3-WT [34]. None of the studies had a TRM of less than 10%, and three (60%) studies had a high TRM over 20% [18, 33, 36] (Table 3). There was no statistically significant difference in the mean ED (including induction death) rates between etoposide-based induction protocols and those that did not use etoposide (28.1% ± 21.9% vs. 35.6% ± 17.4%; $p = 0.513$).

Overall survival (OS) and event-free survival (EFS)

Data on OS was available from 17 studies [17, 31–38, 40–47], and EFS was available for ten studies [17, 18, 31, 32, 34–36, 42, 44, 45], based on different time points of measurement. Excluding the APL-only studies, two studies reported disease-free survivals (DFS) [40, 41]. Most studies reported one-year or two-year OS, which varied from 0 to 78.6% [32, 33, 43, 47] and 7.2–52.6% [17, 31, 36, 41, 46], respectively. Three studies also reported median OS that were between 2.6 months and 8.5 months [32, 43, 47]. The three-year OS was 26.9% for FLT3-ITD and 62.5% for FLT3-WT in one study [35] and ranged between 23% and 37% in three studies [32, 40, 41]. One study reported a four-year OS of 41.9% [44], and two studies reported a five-year OS of 14% and 31.9% [34, 37].

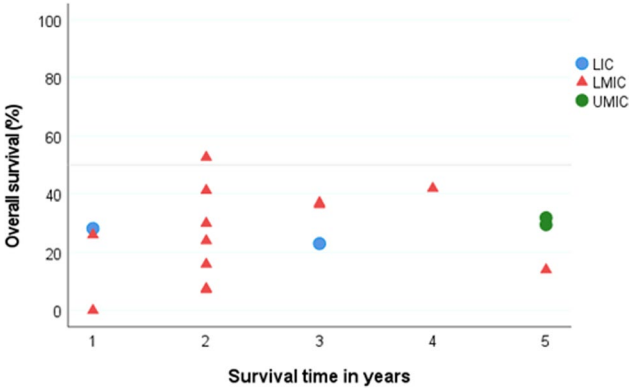


Fig. 2 Overall survival by World Bank income status

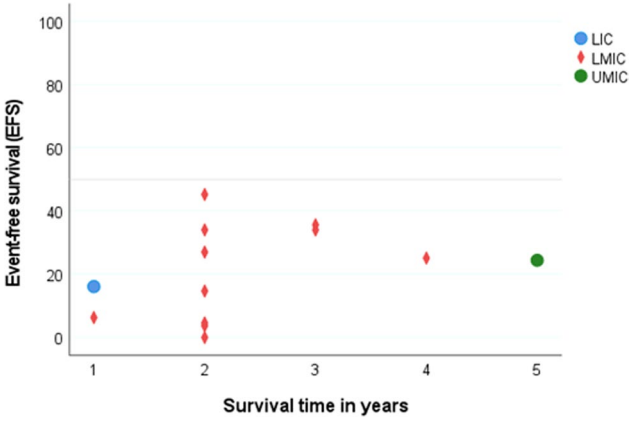


Fig. 3 Event-free survival by World Bank income status

Similarly, most studies reported two-year EFS, which varied from 0.0 to 45.2% [17, 18, 31, 36]. Two studies each reported a one-year EFS of 6.3% and 16.1% [18, 32], and one study reported a four-year EFS of 25.1% [44]. In the study with a one-year EFS of 16.1%, the median EFS was reported to be one month [32]. The three-year EFS was 22.8% for FLT3-ITD and 51.1% for FLT3-WT in one study [35]. One study reported a five-year EFS rate, which was 24.4% [34]. The two studies that reported disease-free survival (DFS) noted two-year DFS of 27% and 34% in one study based on different protocols [41] and three-year DFS of 34% and 35.6% [40, 41].

Risk-stratified outcomes were reported in very few of the studies. Houssou et al. in Morocco reported four-year OS and EFS of 60% each for favourable risks and 40% and 20%, respectively, for unfavourable risks [44]. One other study reported five-year OS and EFS of 44% and 34%, respectively, for favourable risks, and 22.2% and 14.8%, respectively, for unfavourable risks [34]. Maarouf et al. in Egypt reported OS and EFS by post-induction MRD that were 55 ± 17.2% and 49.2 ± 17.1%, respectively, for MRD < 0.1 and 49.7 ± 21.3% and 37.2 ± 20.5%, respectively, for MRD > 0.1 [31] (Table 3).

Etoposide-based induction and survival outcomes

One study that used an etoposide-based induction regimen reported a one-year OS of 26% [47], while the one-year OS was 28.2% and 78.6% in two studies that did not use etoposide [32, 33]. The two-year OS were 41.2% and 52.6% in the two studies that used etoposide-based induction therapy [31, 46] and 7.2% and 10.1% in two of the studies that did not use etoposide [17, 36]. The three-year OS was 23% and 36.4% in two studies that used etoposide-based induction [32, 40], while it was 26.9% and 62.5% for FLT3-ITD and FLT3-WT, respectively, in one study [35]. The three-year OS in one study that did not use etoposide-based induction was 37% [41]. The five-year OS was 31.9% overall in one study that used etoposide-based induction therapy [34], while it was 14% in another study that did not use etoposide-based induction therapy [37] (Table 3). Overall, there was a tendency for a higher OS with etoposide-based induction in a few of the studies, but the limited data does not provide enough evidence to suggest a difference in survival outcome by etoposide use.

OS and EFS varied between studies from the same economic context. When acute promyelocytic leukaemia and cytogenetics risk-stratified outcomes, for those available, are excluded, the overall survival (Fig. 2) and the event-free survival (Fig. 3) rates for children with AML remain low (below 50%) overall.

Treatment abandonment

Data on treatment abandonment rates were available from eight studies and varied from 3.0 to 50.0% (median 12.7%) [17, 18, 32, 34, 36, 37, 43, 46]. The treatment abandonment rate was over 20% in three of these studies [17, 34, 43]. Van Weelderen et al. compared AML treatment outcomes on the standard treatment protocol and the International Society of Paediatric Oncology - Paediatric Oncology in Developing Countries (SIOP PODC), now renamed SIOP Global, low-intensity regimen with a significantly lower abandonment rate on the de-intensified regimen compared to the standard dose-intense regimen (3.0% vs. 19.0%, respectively) [36].

AML relapse and salvage treatment

Relapse rates were reported in 13 studies and ranged between 6.0% and 57% [17, 18, 31, 32, 34–37, 40, 41, 45–47], with 100% mortality in one of the reports [40]. Relapse by risk group was reported by Chellakhi et al. in Morocco and was surprisingly higher for the favourable-risk (22%) compared to the intermediate-risk (4.0%) and unfavourable-risk (16.0%) groups, with an overall relapse rate of 11.0% [46]. Maarouf et al. in Egypt also reported relapse risk by post-induction MRD status, showing a higher risk of relapse in patients with MRD > 0.1%

(46.1 ± 22.1%) compared to those with MRD < 0.1% (30.5 ± 6.1%), with an overall relapse rate of 27.6% [31]. Salvage therapy was reported in four of the studies and involved chemotherapy in two studies [35, 45] and HSCT in two studies [31, 47] (Table 3).

Treatment outcomes of specific AML subtypes

Treatment outcomes of children with APL Eight studies included APL [19, 20, 32–34, 40, 42, 45], of which four evaluated outcomes by APL subtype [33, 34, 42, 45]. Two of the studies included only APL (82 patients) [42, 45]—of which one reported a very high CR of 95%, a low ED rate of 5%, a 10% relapse rate, and a four-year EFS and OS of 75% each [45]. The CR rate in the other APL-only study was 72.6%, with a five-year EFS and OS of 69.4% and 72.5%, respectively, and a total death of 27.4% [42]. Two of the studies reported outcomes for 23 [34] and 4 [33] patients with APL. The CR was very low (13%) in the study with 23 APL patients, with a very high death rate (69.6%) and a low five-year EFS and OS of 26.1% and 30.4%, respectively [34]. In the study with a smaller number of APL, half (50%) of the patients achieved CR, a quarter (25%) of the patients suffered ED, and the one-year OS was 75% [33]. Four of the eight studies did not report disaggregated outcome by APL and non-APL subtypes [19, 20, 32, 40].

Treatment outcomes of children with AMKL

Two studies by Maarouf et al. in Egypt [31] and Cherkaoui et al. in Morocco [37] evaluated treatment in 80 non-DS AMKL patients and 8 AMKL patients, respectively. In the Egyptian study that excluded DS-AMKL [31], the CR was relatively high (71.3%) with a high ED rate of 18.8%, all occurring during induction therapy. Over a quarter (27.6%; 18/65) of the patients relapsed; that varied by MRD status. The two-year OS and EFS were 52.6 ± 12.3% and 45.2 ± 12.3%, respectively (Table 3). In the second study [37], the CR rate was low (43%), the ED rate (37.5%) and relapse rate (28.6%) were high, 12.5% abandoned treatment, and the five-year OS was very low at only 14% (Table 3).

Twenty-two studies were identified in this review across different geographical and income levels within the African continent, with over 2,000 children with AML. Despite a comprehensive search strategy, only a small number of studies, over three-quarters of which were retrospective and single-centre in nature, were included, pointing to the limited published literature on childhood AML in LMICs. There was no unified standard approach for the management of paediatric AML in Africa, with variably unfavourable treatment outcomes, high early deaths, treatment-related mortality, and abandonment.

Discussion

Outcomes of African children diagnosed with AML in these African (LMIC) studies were inferior to those observed in HICs [8, 49] with a high treatment-related mortality [50, 51]. Low post-induction response and survival rates, high early death rates, treatment abandonment, and relapse rates characterise AML treatment in the African setting.

According to international reports, the first incidence peak of AML occurs before the age of one year, with a second peak between the ages of 15 and 20 and a mean age at diagnosis of five years [52]. This review shows that African children are diagnosed with AML at an older age, with mean and median ages 8 years or more in 65% of the reports. Insufficient data have been published to investigate AML treatment and outcomes in infants and young children.

Yet our age-related findings were similar to a study from southern Brazil that documented an older age, with a median age at diagnosis of 10.5 years (range of 0–18 years) [53]– a pattern that resonates with that in other LMICs outside the African region– including Brazil [54], Colombia [55], Mexico [56], India [57], and Pakistan [58]. There was a slight male predominance regarding AML in African children [17–19, 31–33, 35, 36, 39, 40, 42, 44, 46–48]. This trend in male predominance was similar to that reported in Asian context– in Indian [59] and Pakistani [58] studies– and South American context– in Colombian [55] and Brazilian [54] studies– and other LMICs [53]. A similar sex pattern has been reported in high-income countries [8]. This is in contrast to Nordic countries that documented a higher incidence of AML in females [60], suggesting that the epidemiology of AML in children varied in the different geographical regions. While the reason for this difference is not immediately obvious, significant socio-cultural differences may be a key factor.

There was a low rate of risk-based therapy and response assessment based on cytogenetic and molecular prognostic groups in the current review. This reflected the limited capacities to perform cytogenetic and molecular studies in many African settings [17–19, 32, 33, 36, 38, 39, 41, 43]. This contrasts with HICs [8, 61] and other LMICs outside the African region [56, 62]. In a Brazilian study among paediatric oncologists, for instance, cytogenetic and molecular testing were accessible to 85% and 78% of the respondents, respectively [62]. Cytogenetic and molecular genetics are integral components of diagnosis and risk-adapted therapy for AML with prognostic significance [63, 64], greatly contributing to improved survival rates of paediatric AML in HICs [65]. Risk stratification in Africa can identify low-risk patients that can be treated with de-intensified protocols, thereby minimising unacceptably high ED and TRM in African and

other LIC settings. Identification of high-risk stratification informed by cytogenetics and the presence of MRD after induction was likewise limited in African data [66]. Unlike HICs [61, 66] and other LMICs in South America, for example [54, 55], where HSCT has improved the survival outcomes of high-risk patients, HSCT is almost absent in African low-resource settings.

Furthermore, AMKL, an AML prognostic subgroup with an excellent prognosis when associated with Down syndrome (DS-AMKL) but a poor prognosis in non-DS AMKL, was poorly reported on in African literature [12, 25]. Only two studies evaluated outcomes of children with AMKL (one of which excluded children with Down syndrome), with CRs of 43% and 71.4%, respectively [31, 37], which compare relatively well with experiences by the Eastern Europe Cooperative Oncology Group [67]. By contrast, Ruiz-Arguelles et al. previously demonstrated a higher CR rate for patients with AMKL of 73% with aggressive chemotherapy and 84% with low-dose cytarabine [68].

The dose-intense protocols for paediatric AML, of well-controlled clinical trials, resulted in improved outcomes in HICs, with a CR of approximately 90% [69] and ED rates of less than 5% [70, 71]. However, in contrast, the current review found significantly lower CR, as well as poorer EFS and OS on similar regimens in the African context compared to HICs [72, 73]. With the exception of two studies [44, 48], the observed outcomes in the current review were unexpectedly low even for favourable or standard-risk AML. As previously demonstrated, the inferior treatment outcomes of paediatric AML in the current review were closely correlated with the high ED and TRM rates [23, 26]– a pattern similar to that in other LMICs, including Indonesia (ED of 57.1%) [74], India (TRM of 30%) [57], and Pakistan (TRM of 29.4%) [58]. The Medical Research Council Acute Myeloid Leukaemia 12 (MRC AML12) protocol highlighted the disparity in treatment outcome occasioned by the differences in resource context. A randomised trial using this protocol in well-resourced settings was associated with a TRM of only 10% [75], but use of the same protocol in a resource-limited setting in India resulted in a very high TRM of 48% [76]. The above scenario attests to the assertion that "all children with AML should preferably be treated within the context of well-designed clinical trials to ensure the highest quality and safety of management" [77]. However, the reality is far from the real-world context in which most children with AML are treated in the African and other LMIC settings.

The lack of adequate and optimal supportive care, essential for intensive AML treatment, coupled with the high burden of comorbidities like infectious diseases and malnutrition, could lead to high TRM, even for favourable-risk patients on similar regimens in LMICs [78]. While the studies in the current review provide limited insight into the extent to which the degree of supportive care contributed to the observed outcomes, the lack of supportive care has been widely reported as one of the major obstacles to treatment of AML in resource-poor settings, including in Africa [79]. In a Brazilian study, South America [62], a survey among paediatric oncologists found that 54.8% had difficulty in accessing intensive care units. The inevitable consequences are high early death and treatment abandonment rates [80] that compromise survival outcomes. A focus on improving supportive care services, risk-adapted therapy, and addressing the socioeconomic challenges would be crucial to reduce ED and TRM rates in Africa and other LMIC contexts. Otherwise, in the absence of supporting infrastructure, toxicity-related deaths will remain high, and de-intensification may save more lives [81, 82].

Treatment abandonment remains the main challenge in the management of paediatric AML in Africa [15, 83], which was documented in less than half of the studies in this review. This finding might represent an underestimate of the actual burden of abandonment, a problem so common in LMIC settings that it should be systematically reported [84]. Interestingly, two studies in Tanzania and Kenya reported abandonment rates close to those in HICs. However, in two of the seven studies that reported treatment abandonment, it was more than 20%. It is also worth noting that the Kenyan study used a lower-intensity regimen [36], whereas all but one patient in the Tanzanian study experienced early death during therapy [18]. Considering that at least one-third of the survival disparities between HICs and LMICs are attributed to treatment abandonment, efforts towards improved treatment outcomes of AML in LMICs should address this problem [15].

Despite typically high relapse rates, which may be higher when abandonment and loss to follow-up are taken into account, the salvage rate in the current review was exceedingly low and underreported. Only four studies in this review reported salvage therapy, and only two studies offered HSCT as a treatment option [31, 47]. The low salvage rate for relapsed AML in LMIC settings, due to the lack of capacity to offer optimal salvage therapy, including allo-HSCT, has been acknowledged as an important contributor to the inferior treatment outcomes in these settings [23]. While a high relapse rate is a general problem in the treatment of AML even in HICs, with rates averaging about 25–30%, the availability of salvage therapy, including HSCT, meant about 40% of these patients would still survive [11].

The limitation of this review is the small number of eligible studies that were retrospective and single-cantered in nature. Likewise, inconsistent and missing data and a lack of uniform data reporting meant it was not possible

to delineate the aspects of AML treatment and the outcome of specific subtypes. Nonetheless, this review provides an insight into the treatment approaches and outcomes of AML in the African region on which general conclusions can be reached.

Conclusion

Current literature on and management of paediatric AML in Africa was limited, characterised by retrospective studies, inconsistent reporting of outcome data, and underreporting of subgroups. There was great variation in protocols and outcomes, which were inferior, with high TRM and abandonment compared to HICs. Too few studies on resource-adapted management with an aim to reduce TRM have been done. Findings from this review also underscore the need for collaborative adapted management studies and standardised reporting in the African region to improve paediatric AML outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14552-8.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Acknowledgements
The authors would like to acknowledge the authors of the reviewed articles and convey a special tribute to the children whose information made it possible to realize the study's objectives.

Authors' contributions
RN and JvH conceptualized, designed the study, and conducted the literature search. NR analyzed the data and wrote the manuscript. JvH, MK, VS, and NN supervised the study and critically reviewed and revised the manuscript. All authors have read and approved the final manuscript.

Funding
The author(s) reported there is no funding associated with the work featured in this article.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. A protocol was not prepared for this review of literature.

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 20 February 2025 / Accepted: 19 June 2025
Published online: 04 July 2025

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