RESEARCH | Article in Press

Induction failure and early death in paediatric acute myeloid leukaemia in Uganda: a developing country experience

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Received: 1 June 2026 / Accepted: 11 September 2026
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Abstract

Introduction Dose-intensive therapy for paediatric acute myeloid leukaemia (AML) has improved outcomes in high-income countries (HICs); however, outcomes remain poor in resource-limited settings, where induction failure and early death continue to pose significant challenges. This study aimed to determine the frequency of induction failure and early death and identify associated risk factors among children treated for AML in Uganda.

Methods This retrospective study examined induction failure and early death among children with AML. Data collected included demographic information, clinical characteristics, and induction outcomes for children under 18 years who were diagnosed with AML between 2016 and 2022 at three Ugandan institutions. Induction failure was defined as failure to achieve microscopic remission after induction chemotherapy, including deaths during induction. Early death was defined as death before or within 42 days of initiating induction therapy. Variables included sex, age, initial white cell count, and nutritional status, among others. Nutritional status was assessed using the World Health Organization weight-for-height, body mass index (BMI)-for-age, and mid-upper-arm circumference (MUAC) z-scores. Descriptive statistics and logistic regression analyses were performed using IBM SPSS version 27 to investigate variables associated with induction failure and early death.

Results There were 159 children with AML, of whom 87 (54.7%) were males, with a median age of 9.0 years (IQR 3.0–12.0). Nearly half ($n=62$; 39.0%) were malnourished, and over a third ($n=59$; 37.1%) had a peripheral white blood cell count (WBC) at diagnosis of ≥50,000/uL. Of the 149 (93.7%) patients who received induction chemotherapy, 39 (26.2%) experienced induction failure and 27.7% early death (44/159). The main causes of death were sepsis (35%), bleeding (25%), organ failure (15%), severe anaemia (13%), and severe pneumonia with respiratory failure (12%). Induction failure was significantly associated with malnutrition ($p=0.031$), presumed fungal infection ($p=0.043$), and absence of CNS involvement assessment at diagnosis ($p=0.005$). Early death was associated with malnutrition ($p=0.007$), suspected fungal infection ($p=0.008$), and pneumonia ($p=0.024$).

Conclusion In this Ugandan cohort of children with AML, induction failure and early death rates remained high and were strongly associated with infections and treatment-related complications, underscoring the challenges in AML management. Malnutrition, suspected fungal infections, and pneumonia were significantly associated with

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https://doi.org/10.1186/s12885-026-16989-x

Published online: 16 September 2026

poor outcomes, highlighting the need for improved supportive care and early management of complications in resource-limited settings.

Keywords Acute myeloid leukaemia · Induction failure · Early death · Children · Developing country

Introduction

The treatment of paediatric acute myeloid leukaemia (AML) poses a significant challenge, especially in LMICs [1]. Despite the advances in the treatment of AML, a significant proportion of patients fail to achieve complete remission (CR) with the initial induction regimen [2, 3]. In high-income countries (HICs) 5–40% of patients with AML experience induction failure (IF) after standard induction therapy with cytarabine and anthracyclines (AD) because of refractory disease and toxicity [4–6]. This rate is likely to be much higher in LMICs, primarily driven by treatment-related mortality (TRM), supportive care deficiencies, and treatment abandonment [7]. An analysis of five prospective studies that used a more intensive induction regimen comprising idarubicin, cytarabine and etoposide (ICE) reported an IF incidence of 30.8% [8]. Even so, the frequency of occurrence of IF in AML, especially in resource-limited settings, is often underestimated [6].

Early death (ED) rates have markedly reduced in HICs [9], where survival of children with AML treated on the current dose-intense protocol is over 70%. However, ED remains a significant challenge and a major cause of treatment failure in LMICs [6, 7, 10, 11]. The ED rate in patients with AML, reported in the range of 15–46% in LMICs [11–13], is unacceptably high compared to 4.1–5.9% reported in HICs [14–17]. A Central American study reported a TRM of 23%, with the majority (78.5%) of the deaths occurring before or during induction, resulting in an ED rate of 18.3% [18]. In a Tanzanian study, 24 of 25 patients with AML died at a median of 26 days following admission (range, 1 day to 40 weeks), with 21% of the deaths attributed to the treatment-related toxicity [19]. Similarly, in Kenya, the ED rate was reported to be as high as 46% [14]. However, although studies from other African LMICs have reported ED during AML induction, no published Ugandan data describe IF, and evidence on ED in paediatric AML remains limited—a knowledge gap that provides the rationale for the present study.

The lack of response to treatment and ED are considered major causes of poor outcomes in paediatric AML [8] and remain frequent challenges, particularly in low-resource settings [10], where outcomes are consistently inferior to those reported in HICs [20]. Although the high rates of these adverse treatment outcomes in LMICs warrant deliberate, focused attention, to date, ED in particular continues to be a significant cause of treatment failure and poor outcomes in LMICs [7].

Most cases of IF have been attributed to death during induction, commonly resulting from infection and haemorrhage [2, 5], exemplified by an induction mortality of 30.3% among paediatric AML patients in Ethiopia [5]. Older age ≥ 10 years, unfavourable molecular and cytogenetic background, and high white blood cell (WBC) count have been reported as risk factors for IF in children with AML [21, 22], as well as a blast count > 40% at diagnosis [6]. Similarly, haemorrhage, leukostasis and infections have frequently been implicated in the causal pathway of EDs [14]. In a Central American study, up to 40% of treatment-related mortality during remission induction was attributed to infection, which also accounted for 33% of TRM before remission induction therapy and 77% after induction [18]. Despite these findings, data on the prevalence and factors underpinning induction failure and ED in paediatric AML following standard induction therapy in low-resource settings remain limited. Consequently, the true frequency of IF and ED in paediatric AML in these settings is likely underestimated [23].

Reducing toxic mortality, especially EDs, and achieving CR may be important targets to improve the overall survival of children diagnosed with AML in LMICs [24]. Likewise, identification of specific periods of heightened risk, if any, would allow optimization of available supportive care at the most appropriate time during treatment. Accordingly, this study investigated the frequency of IF and ED and associated risk factors in a cohort of children treated for AML in Uganda, a low-income country. This study is, to the best of our knowledge, the first

to characterize both IF and ED and identify factors associated with these outcomes among children with AML treated in Uganda.

Methodology

This was a retrospective cohort study that reviewed manual paper-based records of children and adolescents under 18 years of age diagnosed with and treated for AML at three cancer treatment centres in Uganda from January 2016 to December 2022. These three facilities manage approximately 700 new childhood cancer cases in the country annually. The study population comprised children under the age of 18 years diagnosed with AML at the three paediatric oncology units in Uganda during the study period. All children with a confirmed AML diagnosis within the period were eligible for inclusion. Patients with mixed phenotype leukaemia, mixed lineage leukaemia, or insufficient medical records lacking essential clinical information were excluded. Data were collected on participants' age, sex, baseline CBC, nutrition status, induction response, and cause of mortality if available. Nutritional status was defined according to World Health Organization [WHO] criteria based on weight-for-height, body mass index (BMI)-for-age, and mid-upper-arm circumference (MUAC) z-scores [25]. Nutritional status was classified as normal (z-score > -2 SD), moderately malnourished (z-score < -2 and > -3SD), or severely malnourished (z-score < -3 SD) [25].

The diagnosis of AML was established on blast morphology and percentage of bone marrow aspirates and/or peripheral blood smears with subtyping according to the FAB classification [18] by experienced haematologists. Immunophenotyping by flow cytometry was only available for a small proportion of patients, while cytogenetic and molecular genetic testing were unavailable. Although the diagnostic approach used in the current study context is not equivalent to contemporary diagnostic standards, it reflects the realities of paediatric leukaemia care in many resource-limited settings, where access to advanced diagnostic modalities remains limited. Patients were also evaluated at diagnosis for complete blood counts (CBC) and differentials and central nervous system (CNS) involvement, among others. CNS involvement was defined as more than five leucocytes per microlitre in the cerebrospinal fluid (CSF) with leukaemic cells on cytospin and/or the presence of neurological manifestations, such as cranial nerve palsy [26, 27]. Lumbar puncture for CSF cytospin analysis was not routinely performed in some patients, including those with acute promyelocytic leukaemia (APL), in accordance with institutional clinical practice because of concerns regarding procedure-related bleeding risk.

The induction therapy consisted of the AD protocol, using cytarabine (A), an antimetabolite and pyrimidine analogue, and daunorubicin (D), an anthracycline (*Supplementary Tables 1 and 2*). All chemotherapy regimens were administered as inpatient therapy. All patients received prophylaxis for tumour lysis syndrome (TLS) with hyperhydration and allopurinol, initiated 24 h before the start of chemotherapy. Likewise, all patients received supportive prophylactic medications of cotrimoxazole, fluconazole, acyclovir, and ciprofloxacin. Intensive care unit (ICU) services were not routinely available. All cases of febrile neutropenia were treated as inpatients with broad-spectrum intravenous antibiotics. 'Neutropenia' was defined as an ANC of < 1000 cells/μL. Febrile patients with ANC < 1000 cells/μL were treated with a combination of piperacillin-tazobactam and gentamicin as per the hospital guidelines. Patients were switched to meropenem (where available) if fever continued beyond 48 h. Empirical treatment for fungal infection with Amphotericin B was added if fever continued beyond 96 h [28]. Microbiological investigation for febrile neutropenic patients was limited to only a few cases and was not routine. Blood and blood product transfusions, including whole blood or packed cells, platelets, and fresh frozen plasma, were administered as indicated and when available.

Response to chemotherapy was assessed by bone marrow (BM) morphology on aspirate performed after Day 28 of induction chemotherapy and recovery of blood counts.

Complete remission (CR) was defined as morphological evidence of < 5% leukemic blasts in BM with normal haematopoiesis, no leukaemia cells in peripheral blood or anywhere else, and signs of normal marrow recovery after the induction phase [27].

Induction failure (IF) was defined as non-responsiveness to one induction therapy with > 30% blasts regardless of cellularity or non-achievement of complete remission after two standard induction therapies [6, 29], including patients who died during induction before remission status could be assessed.

Early death (ED) was defined as death before or within the first 6 weeks (42 days) of treatment. ED was further subdivided into two types: ED0–14 for ED before the start of treatment or within the first two weeks (< 15 days) of therapy, which mainly reflected lethal events due to leukostasis and bleeding; and ED15–42 for ED between days 15 and 42 of treatment, which mainly reflected deaths caused by complications from infections during aplasia after induction therapy [7, 14, 26].

IF and ED were considered related but distinct outcomes: IF included refractory disease and death before response assessment, while ED captured early mortality, irrespective of remission status. The purpose of reporting both outcomes was to provide a comprehensive assessment of treatment failure in this setting, where early mortality is an important competing clinical outcome. This overlap may influence interpretation, but we considered both outcomes clinically important because they represent different aspects of treatment failure.

Treatment-related mortality (TRM) is defined as death within 35 days of any of the cycles of chemotherapy (without evidence of an emerging relapse).

Fever was defined as an axillary temperature of 38 °C or higher, which was measured twice on ≥ 2 occasions over a 12-hour period, or an oral temperature ≥ 38.3 °C on a single occasion. Neutropenia was defined as an absolute neutrophil count of < 1000 cells/μL [11].

Febrile neutropenia (FN) was defined according to the Common Terminology Criteria for Adverse Events (CTCAE) as "a disorder characterized by an ANC < 1000 cells/μL and a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour" [30].

Sepsis was defined based on a diagnosis documented by the treating clinician in the patient's medical record, informed by the clinical assessment and available laboratory investigations at the time of care. The investigators did not retrospectively apply standardized diagnostic criteria to classify sepsis.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software package (SPSS for Windows, Version 27.0. Chicago, SPSS Inc.). Categorical variables were summarized as proportions. Numerical data were summarized by mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Binary logistic regression analysis was used to assess the relationship between the primary outcomes and predictor variables. Multiple logistic regression was used for multivariable analysis to assess the factors that independently predicted the outcome variables and was reported as an adjusted odds ratio (AOR) at a 95% confidence level. A two-sided p-value < 0.05 was considered statistically significant. For regression analyses, available-case analysis was performed, and the number of patients included in each analysis was dependent on the availability of the relevant variables and varied according to data availability. Multicollinearity between specific variables (white blood cell [WBC], splenomegaly, and hepatomegaly) was tested using the variance inflation factor (VIF), with a VIF level > 5 considered to indicate multicollinearity [31] and VIF > 10 to indicate serious multicollinearity [32]. Variables that were statistically significant at the bivariable level ($p < 0.05$) and those with p values < 0.2 were included in the multivariable model. IF and ED were analyzed separately as individual outcomes to avoid double counting and misinterpretation, and patients contributing to both outcomes were appropriately accounted for within each respective analysis rather than being counted twice within a single outcome analysis.

Results

There were 159 children identified within the study period and included for analysis. The median age at diagnosis was 9.0 years (IQR 3.0–12.0), with the majority (50.3%, $n = 80$) aged 1-9.9 years. Males constituted over half (54.7%, $n = 87$) of the cohort, with a male-to-female ratio of about 1.2:1. At diagnosis, 62 children (39.0%) were acutely malnourished according to WHO classification criteria, including 30 (18.9%) with moderate acute malnutrition and 32 (20.1%) with severe acute malnutrition. Assessment of CNS involvement at diagnosis was

documented for 96 patients, of whom 14 had CNS involvement, representing 8.8% of the overall cohort. Additionally, 59 patients (37.1%) had a baseline WBC count ≥ 50,000/μL (Table 1).

Treatment-related morbidity among children with AML

One hundred and forty-nine (93.7%) patients received at least one cycle of induction chemotherapy, while 10 (6.3%) did not initiate chemotherapy for reasons that included death before treatment initiation ($n=4$), parental refusal ($n=4$), being too sick ($n=1$), and referral outside the country ($n=1$). The median follow-up time from treatment initiation was 7.2 months (95% CI 4.9–10.0). The most commonly experienced treatment-related morbidities associated with the first induction cycle were related to myelosuppression and included febrile neutropenia ($n=133$; 89.3%), thrombocytopenia ($n=137$; 91.9%), severe anaemia ($n=128$; 85.9%), and bleeding ($n=66$; 44.3%). In the second induction cycle, 91 (61.1%) of the patients developed febrile neutropenia, 82 (54.4%) had thrombocytopenia, 75 (50.3%) had severe anaemia, and 18 (12.1%) had bleeding. Also notable is that at least 38 patients were diagnosed with suspected fungal infections based on clinical and radiological features, as well as their response to treatment (Fig. 1).

Induction failure and early death rates and timing of death

Of the 149 patients who received induction chemotherapy (10 did not initiate chemotherapy for various reasons), 39 (26.2%) experienced induction failure. The ED rate was 27.7% (44/159), including four patients (9.1%) who died before initiation of therapy (Fig. 2A). Notably, half of the EDs among children with AML occurred within the first 14 days following AML diagnosis (Fig. 2B). Early death during induction accounted for the majority of induction failures (71.1%; 27/39).

Infectious complications and haemorrhage were the most common causes of death in children with AML in the current study, being documented in 21 (35.0%) and 15 (25.0%) of the cases, respectively. Organ failure, while of unspecified cause, was another important factor contributing to early death (Table 2).

Patients who experienced induction failure had significantly higher baseline WBC counts compared to those who did not experience induction failure (median 43.91×10^9/L vs. 23.48×10^9/L; $p=0.014$) (Fig. 3A). Similarly,

Table 1 Sociodemographic and clinical characteristics of children with AML in Uganda

Variable	*n*	%
Age (years)		
Median (IQR)	9.0	3.0–12.0
<1	9	5.7
1–9.9	80	50.3
≥10	70	44.0
Sex		
Male	87	54.7
Female	72	45.3
Nutritional status		
Normal	97	61.0
Moderately malnourished	30	18.9
Severely malnourished	32	20.1
CNS involvement at diagnosis		
No	82	51.6
Yes¶	14	8.8
Unknown	63	39.6
WBC count (x10^9/L)		
<50	100	62.9
≥50	59	37.1

IQR Interquartile range, *CNS* Central nervous system, *WBC* White blood cell

¶nine were CSF positive and five had clinical CNS symptoms and signs

https://doi.org/10.1186/s12885-026-16989-x

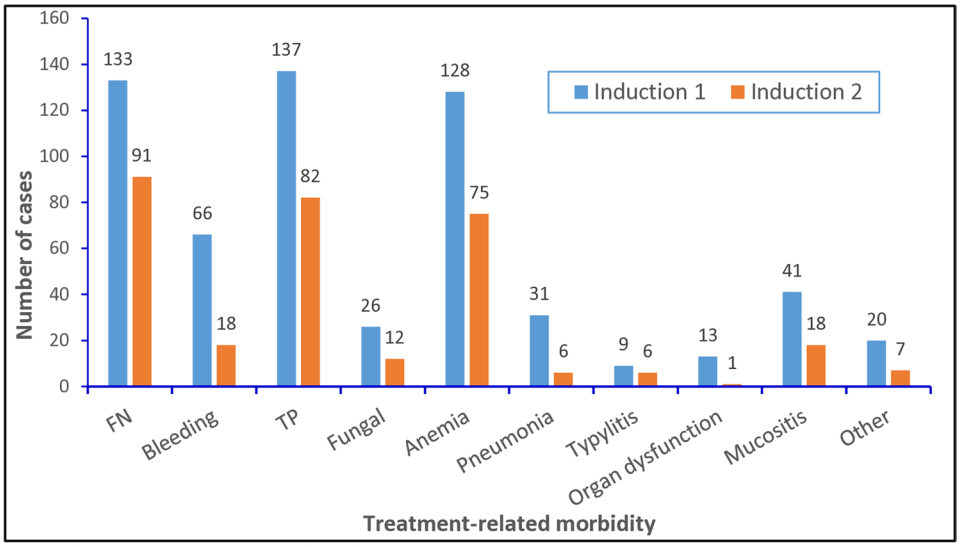

Fig. 1 Treatment-related morbidity among children with AML

FN Febrile neutropenia; TP Thrombocytopenia

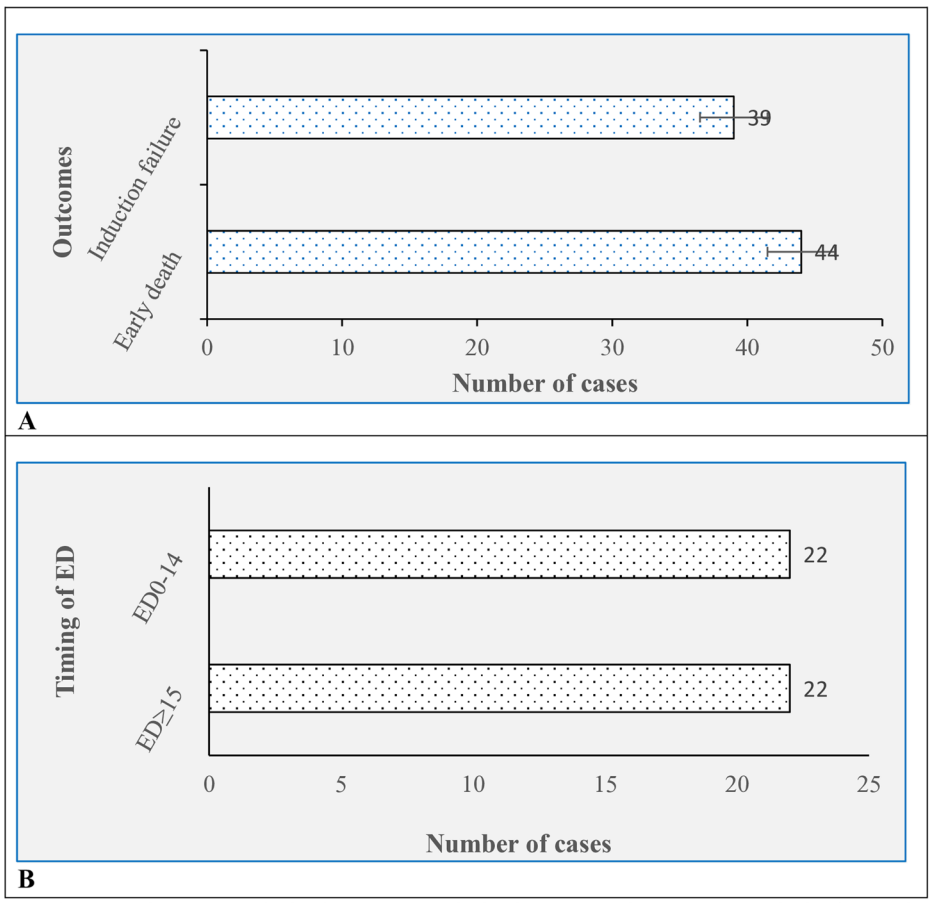

Fig. 2 Induction failure and early death rates, and timing of death. **A** Induction failure and early death. **B** Timing of early death

IF Induction failure; ED Early death; ED0-14 Early death in first 14 days; ED≥15 Early death after day 14

Table 2 Causes of early death in children with acute myeloid leukaemia (AML)

Phase of Early Death	Causes of early death*		
	Total	ED0-14d	ED≥15d
Frequency of events (total)*	**60**	**32**	**28**
Sepsis	21	9	12
Haemorrhage	15	7	8
Organ failure¥	9	9	0
Severe anaemia	8	4	4
Severe pneumonia	7	3	4

*Multiple causes (events) were reported in individual patients; ED0-14d Early death within 0–14 days; ED≥15d Early death after 14 days

¥ (5 Renal, 3 cardiac, and 1 hepatic) of unspecified cause with regard to arising either secondary to severe infections or chemotherapy toxicity

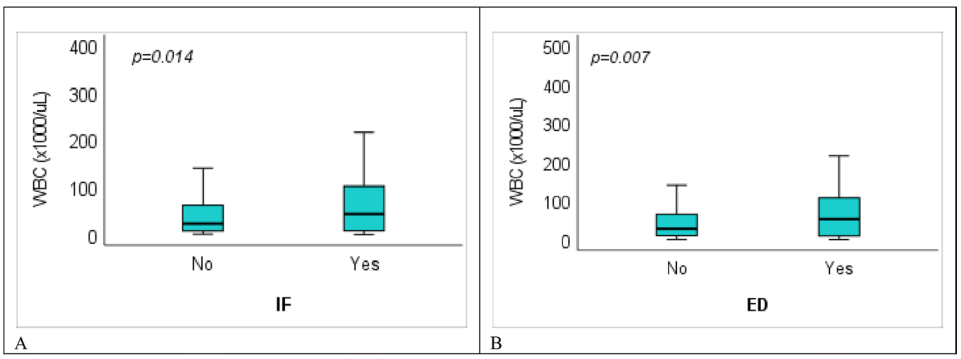

Fig. 3 Box plots of IF and ED with regard to baseline WBC counts. **A** Baseline WBC by IF. **B** Baseline WBC by ED

significantly higher baseline WBC counts were observed for patients who suffered ED compared to those who did not (median 53.16×10^9/L vs. 28.78×10^9/L; $p=0.007$) (Fig. 3B).

Factors associated with induction failure and ED

In bivariable analysis, IF was significantly associated with higher WBC≥50,000/µL ($p=0.040$), fungal infection ($p=0.004$), pneumonia ($p=0.008$), haemorrhage ($p=0.012$), and unknown CNS involvement status ($p=0.002$). Likewise, ED was significantly associated with higher WBC≥50,000/µL ($p=0.039$), malnutrition ($p=0.014$), suspected fungal infection ($p=0.013$), pneumonia ($p=0.002$), tumour lysis syndrome (TLS) ($p=0.046$), haemorrhage ($p=0.025$), organ failure ($p=0.014$), splenomegaly ($p=0.013$), hepatomegaly ($p<0.001$) and unknown CNS involvement status ($p=0.014$) (Table 3).

On multivariable analysis, induction failure was significantly associated with malnutrition (AOR 3.19; 95% CI 1.11–9.14; $p=0.031$), suspected fungal infection (AOR 3.48; 95% CI 1.04–11.67; $p=0.043$), and absence of CNS involvement assessment (AOR 4.63; 95% CI 1.60–13.40; $p=0.005$). Likewise, malnutrition ($p=0.007$), suspected fungal infection ($p=0.008$), and pneumonia ($p=0.024$) were the factors that significantly influenced the occurrence of ED. No multicollinearity was evident between splenomegaly, hepatomegaly, and WBC (a higher count of which can lead to organomegaly)—none of the variables showed a variance inflation factor (VIF) of >5 (Table 4).

Discussion

Induction failure and early death are known to be responsible for poor outcomes of paediatric AML [7, 33], especially in resource-limited settings. Our study shows that nearly one in three children with AML in the current study setting experienced IF and ED following standard induction therapy. The study identifies certain clinical

Table 3 Bivariable Logistic regression of factors associated with induction failure and ED

Variable	IF			ED		
	COR	95% CI	*p*-value	COR	95% CI	*p*-value
Age (years)						
<10	1			1		
≥10	0.70	0.30-1.62	0.399	0.73	0.36-1.49	0.398
Sex						
Male	1			1		
Female	1.46	0.65-3.25	0.362	1.48	0.73-2.96	0.275
WBC ($x10^9$/L)						
<50	1			1		
≥50	2.38	1.04-5.41	0.040*	2.11	1.04-4.28	0.039*
Blast percentage						
<40	1			1		
≥40	1.25	0.41-3.79	0.694	0.70	0.27-1.81	0.467
Extramedullary leukaemia						
No	1			1		
Yes	0.54	0.20-1.47	0.230	0.47	0.18-1.22	0.121
CNS involvement						
No	1			1		
Yes	2.46	0.63-9.67	0.197	1.65	0.46-5.94	0.444
Unknown	4.07	1.70-9.97	0.002*	2.54	1.20-5.35	0.014*
Nutrition status						
Normal	1			1		
Malnourished	1.78	0.79-4.02	0.167	2.43	1.20-4.94	0.014*
Suspected fungal infection						
No	1			1		
Yes	3.67	1.51-8.88	0.004*	2.72	1.23-6.00	0.013*
Pneumonia						
No	1			1		
Yes	3.35	1.37-8.18	0.008*	3.56	1.58-8.02	0.002*
Tumour lysis syndrome						
No	1			1		
Yes	2.38	0.97-5.84	0.059	2.28	1.02-5.11	0.046*
Haemorrhage						
No	1			1		
Yes	2.90	1.27-6.62	0.012*	2.25	1.12-4.56	0.025*
Organ failure						
No	1			1		
Yes	2.03	0.51-8.06	0.316	4.59	1.36-15.46	0.014*
Splenomegaly						
No	1			1		
Yes	1.79	0.83-3.87	0.140	2.47	1.21-5.01	0.013*
Hepatomegaly						
No	1			1		
Yes	1.71	0.79-3.74	0.176	3.44	1.67-7.08	<0.001*

WBC White blood cell, *CNS* Central nervous system

characteristics of children with AML, including malnutrition, suspected invasive fungal infection, absence of CNS involvement assessment, pneumonia, and hepatomegaly, which confer significant risk of IF or ED in resource-limited settings.

The high IF rate observed in the current study of 27% is higher than the 10% rate reported by Pession et al. in the AIEOP AML 2002/01 trial [27] and the 9.7% rate reported by Miyamura et al. in a Japanese cohort [21]. However, findings from other African LMIC settings demonstrate even higher IF rates, including 46% in Kenya

Table 4 Multivariable analysis of factors associated with IF and ED

Variable	IF			ED		
	AOR	95% CI	*p*-value	AOR	95% CI	*p*-value
WBC ($x10^9$/L) [≥50]	1.14	0.30–4.31	0.846	0.74	0.27–2.07	0.570
EML (yes)	-			0.57	0.17–1.98	0.378
CNS involvement (Unknown)	4.63	1.60–13.40	0.005*	2.32	0.92–5.86	0.076
Malnutrition (yes)	3.19	1.11–9.14	0.031*	3.70	1.43–9.58	0.007*
Suspected fungal infection (yes)	3.48	1.04–11.67	0.043*	3.94	1.44–10.80	0.008*
Pneumonia (yes)	2.47	0.85–7.19	0.097	3.07	1.16–8.16	0.024*
TLS (yes)	2.02	0.64–8.36	0.228	1.82	0.48–6.98	0.380
Haemorrhage (yes)	2.42	0.87–6.69	0.090	1.61	0.61–4.24	0.337
Organ failure (yes)	-			3.33	0.71–15.53	0.126
Splenomegaly (yes)	1.50	0.50–4.58	0.478	1.18	0.39–3.60	0.774
Hepatomegaly (yes)	1.28	0.40–4.31	0.676	3.30	1.32–8.26	0.011*

IF Induction Failure, *ED* Early Death, *AOR* Adjusted Odds Ratio, *WBC* White blood cell, *EML* Extramedullary leukaemia, *CNS* Central nervous system, *TLS* Tumour lysis syndrome

*Statistically significant with p-value < 0.05

[13] and 41% in Tunisia [34], highlighting the substantial challenges in achieving successful outcomes with conventional frontline treatment protocols in these settings. The lower IF rates reported from well-resourced settings may partly reflect the use of risk-adapted treatment approaches, better supportive care infrastructure, and greater access to advanced diagnostic and therapeutic resources. The IF rate observed in the present study may, however, represent an underestimate, as a substantial proportion of patients who initiated induction therapy did not undergo post-induction response assessment, partly due to treatment abandonment.

The ED rate in the current study was 28%, representing nearly half (45%) of the total deaths. The observed high incidence of overall and early deaths among our patient cohort aligns with that reported in many LMICs [7, 10]. Data from neighbouring East African countries indicate even more concerning outcomes. In a Tanzanian study, for instance, 24 of 25 children with AML died at a median of 26 days following admission (range, 1 day to 40 weeks), with 21% of the deaths attributed to the toxicity of treatment [19]. Likewise, in Kenya, the ED rate was at a high of 46% [13]. The ED rate observed in the present study is much higher than the 18% reported by Gupta et al. [20] in Central America and is approximately five to nine times higher than the ED rates of 4.1–5.9% reported in HICs [14–17]. These findings suggest that a focus on preventing EDs is indispensable in reducing treatment-related mortality (TRM) and improving outcomes for paediatric AML in LMICs. The stark contrast in death rates compared with HICs further underscores the importance of enhanced supportive care and the availability of well-equipped and adequately prepared centres in managing these high-risk patients.

In our setting, limited access to paediatric intensive care support—including advanced respiratory support, vasopressors, renal replacement therapy, and continuous monitoring—may have contributed to the observed outcomes following severe infection or treatment-related complications. Although intensive care unit availability was not directly assessed in this study, it represents an important contextual factor that may partially explain the high burden of early mortality observed.

Malnutrition emerged as a significant predictor of both IF and ED in the current study. The adverse impact of malnutrition on childhood cancer treatment outcomes, including achievement of induction remission, has been previously documented [28, 35]. For example, in a study by Ghafoor et al. in Pakistan, induction mortality significantly differed by nutritional status, increasing from 19.8% in well-nourished children to 44.7% in severely malnourished patients [28]. This finding may not be surprising, as malnutrition is linked to increased incidence of treatment-related toxicity and morbidity [36, 37]. Malnutrition reduces absorption, decreases drug-protein binding, and impedes oxidative and other metabolic reactions, resulting in an increase in plasma-free drugs and volume of distribution, lower efficacy, a potentially altered treatment response [38], and increased potential for drug-related toxicities. This underscores the importance of implementing targeted nutritional interventions

for high-risk groups. Although resource-limited settings face challenges such as costly therapeutic feeds and supplements and competing healthcare priorities, evidence from Malawi shows that integrating routine nutrition screening, early risk detection, caregiver counselling, and provision of locally available nutrient-dense foods into pediatric care can reduce morbidity and mortality [39].

Infectious complications remain a major challenge in the treatment of paediatric AML, especially in resource-limited settings, and are a significant cause of TRM and other poor outcomes [28, 36]. This is largely attributable to the profound myelosuppressive effects of current dose-intensive chemotherapeutic regimens [14, 16, 17]. In the present study, infections—particularly suspected fungal infections and pneumonia—were significantly associated with poor outcomes, including IF and ED. This finding is consistent with a Central American study, where infections accounted for up to 40% of TRM during remission induction. In the same study, infections were responsible for 33% of TRM before remission induction therapy and 77% after induction [20]. By contrast, studies from HICs have reported relatively lower rates of infectious complications, with clinically and microbiologically documented infections ranging from 9.6% to 29.9% [40, 41]. The prominence of infection-related mortality observed in the present and other previous studies in developing countries [11, 26] likely reflects the inadequacy of supportive care and limited antimicrobial options, compounded by the high burden of infectious diseases in these settings [7, 42, 43]. However, while comorbidities, including HIV, tuberculosis, malaria, and other concurrent illnesses, may influence treatment tolerance, infection risk, TRM, and ultimately IF and ED, these variables were not consistently documented in the retrospective records and therefore could not be reliably incorporated into the analysis. Similarly, the observed associations between outcomes and suspected fungal infections were based on clinical suspicion rather than microbiologically confirmed diagnoses and should therefore be interpreted with caution.

Compared to children with no evidence of CNS involvement, we found that children with undocumented CNS involvement had a significantly higher risk of IF. The impact of CNS involvement on the outcome of children treated for AML has been inconsistent. These discrepancies may be attributed to, among other factors, differences in study context, methodology, definitions of CNS involvement, and therapeutic approaches, among other factors. In the current study, CNS involvement was not assessed in all patients at diagnosis, resulting in missing data that may have influenced the observed association. However, unlike paediatric acute lymphoblastic leukaemia (ALL), CNS3 status in AML has not been documented to affect overall survival and is hence not central to risk stratification [44].

Previous studies have reported a high initial WBC count as a significant contributor to failed induction remission [28, 35] and ED in paediatric AML [45, 46]. For instance, in a Mexican study, children with a WBC>50 × 10^9/L had a 79% increased risk of death [45], while Rubnitz et al. reported a 6% increase in the odds of death during induction for every 10,000-cell increase in leukocyte count [46]. In the present study, baseline WBC count was significantly associated with IF and ED in bivariable analyses, but not after multivariable adjustment, likely reflecting confounding by other disease severity markers and, potentially, limited statistical power due to the relatively small number of outcome events. The absence of multicollinearity with hepatomegaly and splenomegaly suggests that the loss of statistical significance was unlikely to be attributable to redundancy or overlap, despite the biological association between higher WBC counts and organomegaly. While de Morais et al. also reported no relationship between WBC count and risk of death, their findings could have been a result of the small number of patients with high WBC counts at diagnosis and the overall low proportion of patients with recorded WBC in the study [47]. Likewise, our finding may be due to the small sample size and the retrospective nature of the study. While this does not diminish the established prognostic importance of WBC count, it suggests other markers of disease burden may influence its effects. Notwithstanding, hyperleukocytosis remains a therapeutic challenge in LMICs, where supportive care is often inadequate [16], and is associated with increased mortality, leukostasis, tumour lysis syndrome, and poorer survival. In our analysis, baseline leukopenia was not significantly associated with IF or ED, possibly owing to the very small number of cases.

The findings of this study should be interpreted as associations observed in routine clinical practice rather than as evidence of causal relationships, given the inherent limitations of the study design. Nevertheless, the

study provides important real-world, context-specific evidence from a resource-constrained setting, underscoring the value of locally generated data for informing clinical practice, guiding health policy, and prioritising future research.

Strengths and limitations of the study

This study has several important strengths. It was conducted across multiple sites in Uganda, including the national oncology referral centre, enhancing the representativeness and generalizability of the findings. Likewise, the relatively large sample size for a rare paediatric malignancy enhanced the reliability and robustness of the analyses. Furthermore, this study provides the first published Ugandan data on IF and ED in paediatric AML and contributes important context-specific evidence from a setting where such data have been largely unavailable.

However, several limitations should be considered when interpreting the findings. The retrospective study design relied on routinely collected clinical records, making the study susceptible to incomplete, inconsistent, or missing data, which may have reduced the sample size available for certain analyses. In addition, data were obtained from publicly accessible patient files, potentially excluding records that were unavailable or inaccessible and introducing selection bias. Diagnostic limitations also affected the study. Comprehensive molecular testing, cytogenetic analysis, and, in many cases, flow cytometry were unavailable. Consequently, AML diagnosis, based largely on morphology, reflected real-world clinical practice in a resource-limited setting rather than universal immunophenotypic confirmation, with the potential for diagnostic uncertainty and misclassification bias. The absence of these investigations also prevented adjustment for important biological risk factors that may influence treatment response. Missing documentation of CNS involvement, limited microbiological investigations, and frequent reliance on clinical diagnoses may have resulted in under-recognition or misclassification of infectious complications, including sepsis. In addition, inconsistent documentation of baseline comorbid conditions may have resulted in residual confounding. The overlap between IF and ED may also have affected comparisons of their frequencies. Finally, incomplete and inconsistent documentation, unmeasured confounders, and variable diagnostic capacity—challenges inherent in retrospective studies conducted in LMICs—may have influenced the observed associations and precluded causal inference.

Nevertheless, the study provides important real-world insights into pediatric AML outcomes within the realities of routine cancer care in Uganda and offers a valuable foundation for future prospective studies with more comprehensive diagnostic and clinical data collection.

Conclusions

The present study identifies risk factors associated with IF and demonstrates that early deaths, including those occurring during induction, remain a major challenge in the treatment of paediatric AML in developing countries, accounting for a substantial proportion of all mortality. These findings support the implementation of structured early-warning criteria to guide hospital readmission decisions and prompt initiation of appropriate therapy during the induction period, with the goal of reducing preventable early mortality. Future studies should also evaluate prophylactic and therapeutic strategies for better management of haemorrhagic complications and bacterial or fungal infections.

Abbreviations

AD	Cytarabine-Daunorubicin
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count

CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
ED	Early death
FN	Febrile neutropenia
HIC	High-income country
ICE	Idarubicin-Cytarabine-Etoposide
IF	Induction failure
IQR	Interquartile range
LMIC	Low-and middle-income countries
TP	Thrombocytopenia
TRM	Treatment-related mortality
WBC	White blood cell

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1186/s12885-026-16989-x.

Acknowledgements The authors would like to convey a special tribute to the children whose information made it possible to realize the study's objectives. The authors also acknowledge the invaluable support of the staff and management of the Uganda Cancer Institute, Mulago National Specialized Hospital, and Mbarara Regional Referral Hospital, with special appreciation extended to the staff of the Departments of Paediatric Oncology at all three study sites.

Authors' contributions RN conceptualized and initiated the study, and contributed to the study design, data collection, and interpretation of results. JvH, JBK, MK, NN, SV contributed to the design, supervised the study, and reviewed the draft manuscript, and critically revised the manuscript. BA supervised the study and critically revised the manuscript. All authors have read and approved the final manuscript.

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

Data availability All data relevant to the study are included in the article or uploaded as supplementary information. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate All methods were carried out in accordance with relevant guidelines and regulations, and the study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Uganda Cancer Institute Research and Ethics Committee (UCI-2024-97). The requirement for written informed consent and assent was waived by the ethics committee due to the retrospective data collection and no risk.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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