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# A retrospective review of paediatric acute myeloid leukaemia at Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa

**de Jager, Rika Leonora**

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# A Retrospective review of paediatric acute myeloid leukaemia at Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa

Dr Rika Leonora de Jager (Leonie)
Student nr: 449655
MBBCh (Wits)
DCH
BSc Medical Sciences (UP)

SUPERVISOR:
Dr Mairi Bassingthwaighte
MBBCh (Wits)
FC(Paed)SA
Certificate of Oncology

A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand in fulfilment of the requirements of a Masters in Medicine for Paediatrics (MMed degree)

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## Declaration: Student's contribution to article and agreement of co-author

I, Rika Leonora de Jager, student number 449655, declare that this Research Report is my own work and that I contributed adequately towards research findings in the article stated below which are included in my Research Report.

**Signature of Student** ……  …….

**Date**…17/03/2022…….

**Name of Primary Supervisor:** Mairi Bassingthwaighte

**Signature of Primary Supervisor** ……  …….

**Date**……17/03/2022……..

**Agreement by co-authors:** By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

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| Authors | Name | Signature | Date |
|---|---|---|---|
| **1st author** | Rika Leonora de Jager |  | 17/03/2022 |
| **2nd author** | Mairi Bassingthwaighte |  | 17/03/2022 |
| **3rd author** | | | |
| **4th author** | | | |
| **5th author** | | | |
| **6th author** | | | |

**Comments by primary supervisor:** This research was presented as a poster presentation at the SIOP 2021 congress held virtually from 21 to 24 October 2021. It was also presented as an oral presentation at the Paediatric Research day 2021 on 2 December 2021.

……
……

## Dedication

I would like to dedicate this research report to my husband and my mother.
Their unwavering support and selfless sacrifices made this possible.

## Acknowledgements

I would like to express my sincere gratitude to my supervisor, Dr Mairi Bassingthwaighte for all her guidance, time and expertise! I would also like to thank Prof Kebashni Thandrayan for the help with the Kaplan Meier curves and some statistics. I would also like to extend my thanks to Dikopo Fihla for help with locating some files and following up on some patient outcomes as well as to the Department of Paediatric Haematology & Oncology at the Chris Hani Baragwanath Academic Hospital for allowing me to do the study in their department.

And most importantly, to our patients and their parents. We will always strive to serve you better.

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## List of Abbreviations

ADE – Cytarabine (100 mg/m2), Daunorubicin (60 mg/m2), Etoposide (150 mg/m2)

AML – Acute Myeloid Leukaemia

APL – Acute Promyelocytic Leukaemia

ATRA – All-trans retinoic acid

BMAT – Bone marrow aspiration and trephine

BFM – Berlin-Frankfurt-Munster

CDW – Central Data Warehouse

CHBAH – Chris Hani Baragwanath Academic Hospital

CNS – Central Nervous System

CR – Complete Remission

FAB – French-American-British Classification

HAM - High-dose cytarabine (3 g/m2)/mitoxantrone (10 mg/m2)

HIC – High-income countries

HREC – Human Research Ethics Committee

HSCT – Haematopoietic stem cell transplant

ICU – Intensive Care Unit

LMIC – Lower- and middle-income countries

MDS – Myelodysplasia

MRD – Minimal Residual Disease

NHLS – National Health Laboratory Service

PICU – Paediatric Intensive Care Unit

PR – Partial Remission

SIOP PODC – International Society of Pediatric Oncology, Pediatric Oncology in Developing Countries

WCC – White Cell Count

# A Retrospective review of paediatric acute myeloid leukaemia at Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa


## Abstract

**Background and Aims:** Survival gains in paediatric acute myeloid leukaemia (AML) in high-income countries (HIC) have not been mirrored in low- and middle-income countries (LMIC). This study aimed to determine the disease spectrum, outcome and complications of paediatric AML in a resource constrained oncological service in Johannesburg, South Africa.

**Methods**: From 1998 to 2017, the clinical details, treatment, outcome and complications of all paediatric patients with AML were analysed. Treatment was according to the Berlin-Frankfurt-Munster (BFM) AML 1998 protocol.

**Results**: Over the 20-year study period 119 children, with a mean age of seven years, were diagnosed with AML. Fifty (42%) were classified as standard risk and 54 (45%) as high risk. Included in the cohort, were 23 patients diagnosed with Acute Promyelocytic Leukaemia (APL). Eighty-four (71%) patients died: 55 (65%) deaths were due to disease-related causes and 29 (35%) were due to sepsis. Forty-one (49%) of the deaths had occurred by the end of first induction. Infections during treatment were found in 93 (78%) patients and sepsis-related deaths increased from 19% to 29% over the two decades (p-value 0.29). Overall survival was 32% with an event free survival of 24%. The five-year survival rate for children with APL was 30%.

**Conclusion**: Paediatric AML survival was poor, with no improvement over the two decades. Induction and sepsis related mortality rates are unacceptably high. This data will be used to guide strategies to improve survival of paediatric AML in our setting. Targeting early mortality and children with APL have the potential for significant benefit.

## Introduction

Acute myeloid leukaemia (AML), the second most common childhood leukaemia, comprises about seven percent of all childhood cancers and 25% to 33% of all forms of leukaemia in patients under 14 years of age.[1,2] AML is a group of heterogeneous diseases with different biological subtypes and very poor prognosis historically. The 5-year survival rates of AML in high-income countries (HIC) have improved markedly from 21% in 1979 to 75% in 2009.[3,4] These survival gains are due to improved supportive care, intensified risk-stratified chemotherapy, the use of minimal-residual disease (MRD) monitoring and stem cell transplantation.[3]

Treatment of AML in resource poor settings is challenging because of the intensity of chemotherapy protocols, late presentation, lack of supportive care facilities, high cost of treatment and poor access to stem cell transplantation.[3] Van Weelderen et al[5] underscored the need for more data from low- and middle- income countries (LMIC) in a recent systematic review of paediatric AML outcomes. A study conducted in 2016 in India reported an overall survival of 36% (26 out of 72 patients) and a 2010 study in China, documented a seven-year survival of 33% (61 of 185 patients).[6,7] This suggests that LMIC have not observed the same improvement in survival as HIC. Song et al. in Republic of Korea showed that improved survival is possible, with a five-year survival rate of 70%, following similar strategies as that of other HIC.[3]

In South Africa, Stones et al reported a survival rate of 52.1% for all childhood cancers and 48.8% for leukaemia.[8] A detailed analysis of paediatric AML has not been conducted in South Africa. Describing AML and the specific aspects of the disease in this resource-constrained setting should provide a better understanding of factors (both clinical and demographic) influencing survival. This knowledge will be used to identify and address deficits in care to improve survival and quality of life for our patients.

We conducted a retrospective review of all AML presenting to or managed in the paediatric oncology unit of Chris Hani Baragwanath Academic Hospital (CHBAH) in Johannesburg, South Africa.

## Methods

A retrospective, cohort study was performed on all paediatric AML patients, from birth to 18 years of age, diagnosed between 1 January 1998 to 31 December 2017 at the Chris Hani Baragwanath Academic Hospital (CHBAH) Paediatric Oncology Unit. This unit provides a tertiary service for the care of children from Gauteng and North West, including neighbouring countries, Botswana, Eswatini and Zimbabwe. The unit receives on average 130 newly diagnosed paediatric cancer cases annually and has 600 out-patient visits monthly. Furthermore, hospital permission has been granted enabling the unit to accept teenagers up to 18 years of age which is beyond the 14-year age cut-off applicable to the general paediatric wards at CHBAH. Paediatric allogeneic haematopoietic stem cell transplant (HSCT) is not available in our centre. Intensive chemotherapy is the mainstay of treatment for AML, and the Paediatric Oncology Unit at CHBAH has adopted the Berlin-Frankfurt-Munster (BFM) protocol for the treatment of AML (Figure 1).

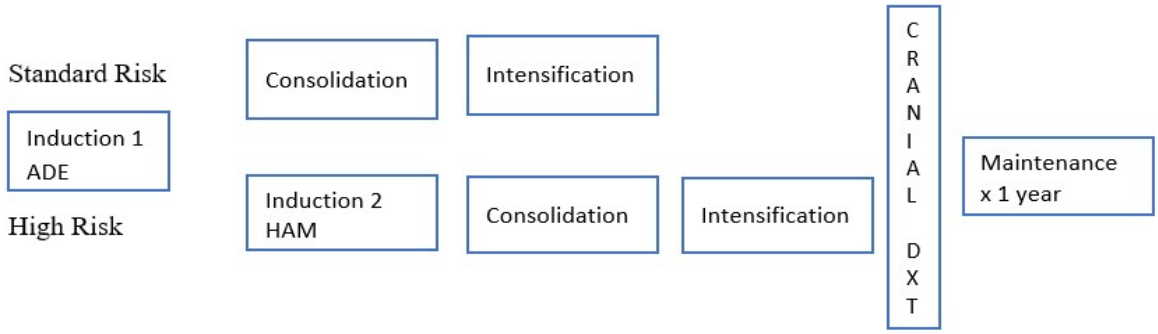


*Figure 1: BFM AML 1998 protocol overview*[9]

All patients were risk stratified based on cytogenetics, immunophenotyping, molecular genetics and/or the French-American-British (FAB) classification. Standard/favourable risk included core binding factor (CBF)- t(8;21), inv(16) and PML-RARA t(15;17) and high risk included t(8;16), t(9;22), inv(3) and complex karyotypes amongst others. Cytogenetics that did not fall into either group were classified as intermediate risk.[7,10] If no cytogenetics were available the FAB Classification was used with M3, M1/2 Auer and M4eos being standard risk. FAB Classes M0, M4, M5, M6 and M7 were all high risk.

Central Nervous System (CNS) disease was defined as having more than five leucocytes/µL on cerebrospinal fluid with blasts or neurological symptoms or intracranial infiltrates on neuroimaging.

**Cytoreductive pre-phase:** (give if WCC >50 x $10^9$/L ± large organomegaly or clinical hyperleukocytosis syndrome): Thioguanine orally (PO), Cytarabine intravenous/subcutaneous

(IV/SC) with or without the addition of Hydroxyurea orally (PO). If there is no noticeable decrease in blasts by day 3, then induction is commenced. **Induction ADE**: Cytarabine, Daunorubicin, Etoposide. (No availability of Idarubicin in our setting). **2nd Induction HAM:** high-dose Cytarabine, Mitoxantrone. **Consolidation**: 6-week therapy consisting of seven different drugs: 6-Thioguanine orally; Prednisone orally; Vincristine; Cytarabine; Doxorubicin; Intrathecal (IT) (age-dependent dose) Cytarabine; Cyclophosphamide. **Intensification (HAE)** high-dose Cytarabine, Etoposide. **Maintenance therapy:** Initially CNS maintenance weekly Cytarabine Intrathecal (IT) (age-dependant dose) x 4 weeks, concurrent with CNS irradiation (age-dependant dose) with Thioguanine orally (PO) and Cytarabine every 4 weeks. **Acute Promyelocytic Leukaemia (APL) modifications**: ATRA therapy commenced immediately and induction chemotherapy initiation determined per WCC. APL only receives ADE induction, consolidation and 1 HAE block prior to commencing maintenance.[9]

Patients who had a provisional diagnosis of leukaemia or AML were identified from the admission book at the Paediatric Oncology Unit. Patients who were diagnosed with Down syndrome, myelodysplasia, therapy-related AML or who were referred to a different hospital for treatment were excluded. Of the 154 patients identified, 35 were excluded: 11 had Down Syndrome, two had myelodysplasia (MDS), 17 were diagnosed with a different malignancy, two were treated at another facility, no files could be found for two patients and one was a duplicate entry (Figure 2). Data was extracted from the hospital and separate oncological records. Data of the remaining 119 patients were then entered into a REDCap database. Data captured included demographic details, clinical details, treatment, complications and outcomes. The NHLS provided all laboratory results conducted by them for AML patients during that time period from the Central Data Warehouse (CDW). Once data was collected, it was exported into an excel spreadsheet, cleaned and then analysed using STATISTICA 13.5.0.17. Categorical variables were expressed as frequencies and percentages and the Fischer exact and Chi square tests were used for bivariate analyses. The mean, standard deviation or median were used for continuous variables. Survival analysis was done using Kaplan Meier Curves.

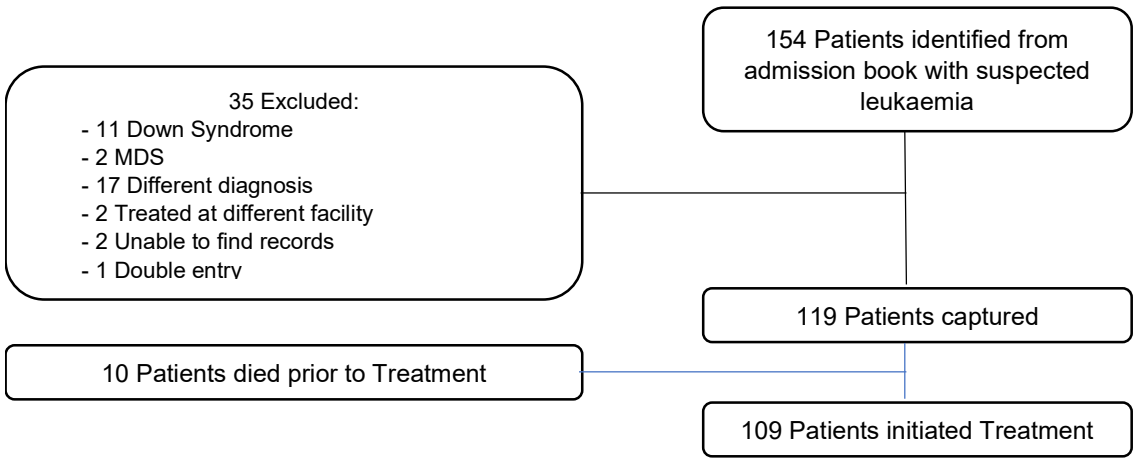


***Figure 2**: Patient Consort Diagram*

Overall survival referred to patients being alive at the end of the study, event free survival was defined as: no relapse or secondary malignancy as well as death not occurring. Disease-related deaths were defined as any complication from AML leading to death such as relapse or bleeding in the absence of infection or signs of sepsis. Early death rate is defined as death within 42 days of diagnosis. Patients who did not complete treatment for any reason were considered to have abandoned treatment. Complete remission was defined as less than five percent blasts on bone marrow, absence of blasts with Auer rods or absence of extramedullary disease.[10] Partial remission (PR) was defined as having between five percent and 15% blasts on bone marrow morphology after induction. More than 15% blasts on bone marrow morphology were defined as resistant disease.

Infection during treatment was only captured if culture confirmed and if it was treated with antimicrobials. If death resulted from such an infection or if sepsis was present at death, it was recorded as a sepsis-related death. Culture negative septic episodes were not included. Fluconazole and Trimethoprim-sulfamethoxazole are given prophylactically to all patients with AML in the unit.

Any blood products including packed red cells, fresh frozen plasma and platelets, were regarded as a blood and blood product transfusion.

Permission to conduct the study was obtained from the Chief Executive Officer of CHBAH and the Head of Department of the Paediatric Oncology Unit, as well as the National Health

Laboratory Service (NHLS) and the Human Research Ethics Committee of the University of the Witwatersrand (HREC).

## Results

One hundred and nineteen (119) patients were diagnosed with AML over the 20-year study period (Table 1). The mean age was seven years, males comprised 53 (45%) and females 66 (55%). CNS disease was detected in seven (6%) patients at diagnosis. On presentation, the mean white cell count (WCC) was 58.4 x $10^9$/L, the mean platelet count 59 x $10^9$/L and the mean haemoglobin was 6.5 g/dL. One hundred and ten patients (92%) received a blood or blood product transfusion at least once, with a mean of 30 transfusions per patient.

***Table 1:*** *Baseline Characteristics*

| General Characteristics | N | % |
|---|---|---|
| **Total** | **119** | **100.0** |
| **Gender** | | |
| Males | 53 | 44.5 |
| Females | 66 | 55.5 |
| **Age** | | |
| Infants (0 - 12 months) | 18 | 15.1 |
| Pre-schoolers (>1 - 5 years) | 30 | 25.2 |
| Young children (>5 yrs - 10 yrs) | 43 | 36.1 |
| Older children (>10 yrs - 13 yrs) | 21 | 17.6 |
| Teenagers (>13 yrs - 18 yrs) | 7 | 5.9 |
| **FAB Classification** | | |
| FAB Classification - M0 | 6 | 5 |
| FAB Classification - M1 | 4 | 3.4 |
| FAB Classification - M2 | 31 | 26.1 |
| FAB Classification - M3 | 23 | 19.3 |
| FAB Classification - M4 | 12 | 10.1 |
| FAB Classification - M4eos | 1 | 0.8 |
| FAB Classification - M5 | 24 | 20.2 |
| FAB Classification - M6 | 2 | 1.7 |
| FAB Classification - M7 | 9 | 7.6 |
| Other | 7 | 5.9 |
| **Risk Profile** | | |
| Standard Risk | 50 | 42 |
| Intermediate Risk | 7 | 5.9 |
| High Risk | 54 | 45.4 |
| Unknown | 8 | 6.7 |
| **Clinical characteristics at Diagnosis** | | |
| Hepatomegaly | 78 | 65.5 |
| Splenomegaly | 45 | 37.8 |
| Lymphadenopathy | 64 | 53.8 |
| Bleeding diathesis | 54 | 45.4 |
| CNS Involvement | 7 | 5.9 |

| | | |
|---|---|---|
| No CNS Involvement | 83 | 69.7 |
| CNS Unknown | 29 | 24.4 |
| WCC <50 x $10^9$/L | 77 | 64.7 |
| WCC ≥50 x $10^9$/L and <100 x $10^9$/L | 18 | 15.1 |
| Hyperleukocytosis (≥100 x $10^9$/L) | 23 | 19.3 |
| Platelets < 20 x $10^9$/L | 33 | 27.7 |
| **Nutrition** | | |
| Normal weight-for-height (wt-for-ht ≥-2 and ≤+2) | 72 | 60.5 |
| Severely underweight (Wt-for-age <-3) | 10 | 8.4 |
| Severely Wasted (Wt-for-ht <-3) | 7 | 5.9 |
| Severely Stunted (Ht-for-age <-3) | 19 | 16 |

**Classification**

The risk profile distribution comprised 50 (42%) standard-risk and 54 (45%) high-risk, with 7 (6%) classified as intermediate risk. Using the FAB classification, M2 was the most frequent, 31 (26%), followed by M5, 24 (20%). Twenty-three (19%) were diagnosed with Acute Promyelocytic Leukaemia (APL) or M3 (Table 1).

**Poor Prognostic Features**

Twenty-eight (24%) patients were over 10 years of age and of them, 16 (57%) died. Ten patients (8%) were severely underweight for age, nine died (90%) and one severely underweight patient survived (p-value 0.29). No one was obese. Twenty-three patients (19%) had hyperleukocytosis and 13/119 (11%) had resistant disease following the first ADE induction chemotherapy. Eighteen out of the 23 patients with hyperleukocytosis died (78%). Thirty-nine of the 53 males (74%) died, compared to 45/66 females (68%). Thirteen males (25%) achieved complete remission after ADE compared to 29 females (44%). Thirty-three (28%) patients presented with a platelet count of less than 20 x 109/L, of whom 23 (70%) achieved complete remission and 14 died (42%). Seventy-eight patients (66%) had hepatomegaly, of whom 53 (68%) died and 26 (33%) achieved complete remission. Twenty-four patients (20%) had M5 FAB morphology, of whom only seven (29%) achieved complete remission after ADE and 23 (96%) died (Table 3). A logistical regression analysis was done trying to determine the predictability of poor prognostic factors on outcome, however the only significant factor was age, with an odds ratio of 0.89 (p value: 0.019).

**Complications**

Of the 109 patients who started treatment, 93 (85%) had culture-confirmed infection during their course of treatment. Of these patients who had infection, 58 died (62%), 31 from disease-related causes (which would include any complication of the disease itself excluding sepsis)

and 27 from sepsis-related causes. There was a total of 201 septic episodes as some patients became septic more than once during their treatment. Gram positive bacilli were cultured 37 (18.4%) times, gram positive cocci 70 (34.8%) times and gram negative bacilli 67 (33.3%) times. Twenty-five (12.4%) episodes of fungal sepsis were found and two (1%) culture-confirmed viruses. Comparing the first and second decades, 38 patients (72%) had infection during treatment between 1998 and 2007 and 55 patients (83%) had infection between 2008 and 2017 (p-value 0.1924) (Table 4). Fifteen patients (13%) were admitted to the intensive care unit (ICU) at least once and of them, nine died (60%) by the end of the study.

**Outcomes (Figure 3)**

Overall survival was found to be 29% (35) (Table 3, Figure 4). Included in this number are six patients who were lost to follow up and could not be reached to confirm their outcome. They are thought to be alive, as they completed most of their treatment and were well at their last visit. Eighty-four (71%) patients died, of which 55 (65%) were due to disease-related causes and 29 (35%) due to sepsis (Table 2). Event-free survival was found to be 24%. Thirty-seven patients (31%) did not complete treatment and of them only two (5%) survived. Both of the survivors abandoned treatment during maintenance. A further 22 patients abandoned treatment during maintenance, all of them died. Five abandoned treatment and died before the initiation of HAM, only one abandoned treatment before ADE and three before first intensification.

Of the 54 patients who were classified as high risk, 44 died (81%) versus 29 (58%) of the 50 classified as standard risk. The early death rate, was 38 (32%) and relapse, after either complete or partial remission, occurred in 28 (24%) patients. Partial remission (PR) was seen in 17 (14%) patients after ADE induction and complete remission (CR) in 42 (35%). Resistant disease was observed in 13 (11%) patients.

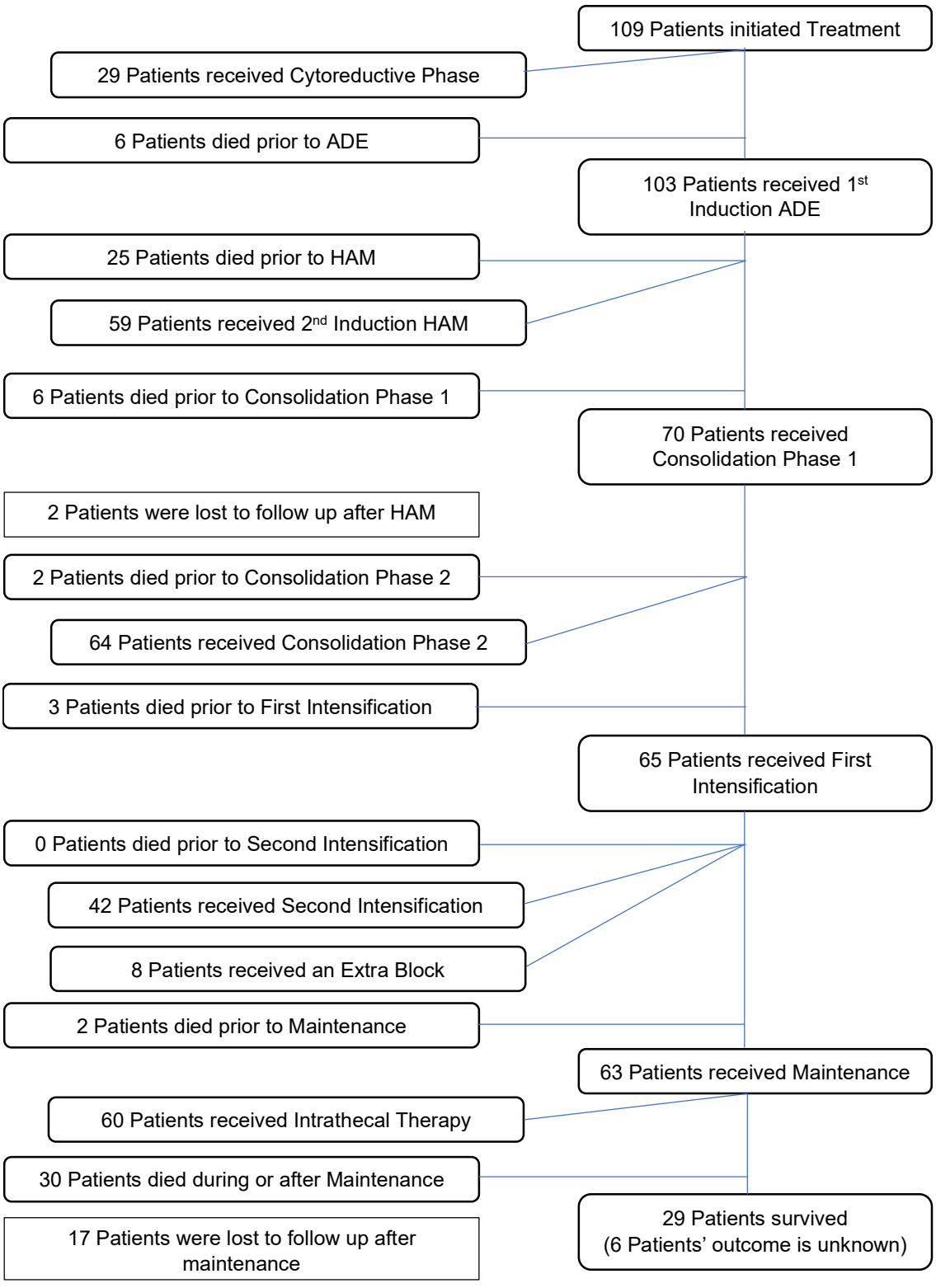


***Figure 3**: Patient Outcomes*

***Table 2**: Treatment and Outcomes*

| | N | % |
|---|---|---|
| **Total** | 119 | 100 |
| **Treatment received** | 109 | 91.6 |
| **Complications** | 105 | 88.2 |
| Infection during treatment | 93 | 78.2 |
| Total culture-confirmed septic episodes | 201 | |
| *Gram positive bacilli* | 37 | 39.8 |
| *Gram positive cocci* | 70 | 75.3 |
| *Gram negative bacilli* | 67 | 72 |
| *Fungus* | 25 | 26.9 |
| *Virus* | 2 | 2.2 |
| Profound neutropaenia (Absolute neutrophil count <0.5 x $10^9$/L) | 92 | 77.3 |
| Prolonged, profound neutropaenia (>7 days) | 89 | 74.8 |
| ICU Admissions | 15 | 12.6 |
| **Outcome** | | |
| Overall survival | 35 | 29.4 |
| 5-year overall survival | 38 | 31.9 |
| Early death rate (within the first 42 days) | 38 | 31.9 |
| Loss to follow up | 19 | 16.0 |
| Relapse | 29 | 24.4 |
| Treatment abandonment | 37 | 31.1 |
| Deaths | 84 | 70.6 |
| Disease-related deaths | 55 | 46.2 |
| Sepsis-related deaths | 29 | 24.4 |

***Table 3:*** *Survival and Deaths*

| | N | Complete Remission | | Event-free Survival | | 5-year Survival | | Deaths | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % |
| Total | 119 | 42 | 35.3 | 29 | 24.4 | 38 | 31.9 | 84 | 70.6 |
| Gender | | | | | | | | | |
| Male | 53 | 13 | 24.5 | 11 | 20.8 | 15 | 28.3 | 39 | 73.6 |
| Female | 66 | 29 | 43.9 | 18 | 27.3 | 23 | 34.8 | 45 | 68.2 |
| Age | | | | | | | | | |
| <1 yr old | 18 | 8 | 44.4 | 1 | 5.6 | 2 | 11.1 | 16 | 88.9 |
| 1 - 5 yrs old | 30 | 8 | 26.7 | 8 | 26.7 | 11 | 36.7 | 21 | 70 |
| >5 - 10 yrs old | 43 | 14 | 32.6 | 11 | 25.6 | 13 | 30.2 | 31 | 72.1 |
| >10 - 13 yrs old | 21 | 9 | 42.9 | 7 | 33.3 | 9 | 42.9 | 12 | 57.1 |
| >13 - 18 yrs old | 7 | 3 | 42.9 | 2 | 28.6 | 3 | 42.9 | 4 | 57.1 |
| WCC/$mm^2$ | | | | | | | | | |
| < 50 000 | 77 | 30 | 39 | 20 | 26 | 27 | 35.1 | 53 | 68.8 |
| 50 000 – 100 000 | 18 | 6 | 33.3 | 5 | 27.8 | 6 | 33.3 | 12 | 66.7 |
| >100 000 | 23 | 6 | 26.1 | 4 | 17.4 | 5 | 21.7 | 18 | 78.3 |
| Platelets | | | | | | | | | |
| < 20 x $10^9$/L | 33 | 14 | 42.4 | 8 | 24.2 | 10 | 30.3 | 14 | 42.4 |
| CNS involvement | | | | | | | | | |
| Yes | 7 | 3 | 42.9 | 0 | 0 | 2 | 28.6 | 5 | 71.4 |
| No | 83 | 36 | 43.4 | 24 | 28.9 | 31 | 37.3 | 55 | 66.3 |
| Unknown | 29 | 3 | 10.3 | 5 | 17.2 | 5 | 17.2 | 24 | 82.8 |
| Clinical Characteristics | | | | | | | | | |
| Hepatomegaly | 78 | 26 | 33.3 | 19 | 24.4 | 28 | 35.9 | 53 | 67.9 |
| Weight-for-age < -3 | 10 | 2 | 20 | 0 | 0 | 1 | 10 | 9 | 90 |
| Risk Profiles | | | | | | | | | |
| Standard Risk | 50 | 17 | 34 | 17 | 34 | 22 | 44 | 29 | 58 |
| Intermediate Risk | 7 | 2 | 28.6 | 3 | 42.9 | 3 | 42.9 | 4 | 57.1 |
| High Risk | 54 | 22 | 40.7 | 8 | 14.8 | 12 | 22.2 | 44 | 81.5 |
| Unknown Risk | 8 | 1 | 12.5 | 1 | 12.5 | 1 | 12.5 | 7 | 87.5 |
| FAB Subtypes | | | | | | | | | |
| M0 | 6 | 2 | 33.3 | 2 | 33.3 | 2 | 33.3 | 4 | 66.7 |
| M1 | 4 | 1 | 25 | 1 | 25 | 2 | 50 | 2 | 50 |
| M2 | 31 | 18 | 58.1 | 13 | 41.9 | 17 | 54.8 | 16 | 51.6 |
| APL - M3 | 23 | 3 | 13 | 6 | 26.1 | 7 | 30.4 | 16 | 69.6 |
| M4 | 12 | 5 | 41.7 | 2 | 16.7 | 3 | 25 | 9 | 75 |
| M4eos | 1 | 0 | 0 | 1 | 100 | 1 | 100 | 0 | 0 |
| M5 | 24 | 7 | 29.2 | 1 | 4.2 | 1 | 4.2 | 23 | 95.8 |
| M6 | 2 | 2 | 100 | 0 | 0 | 0 | 0 | 2 | 100 |
| M7 | 9 | 4 | 44.4 | 2 | 22.2 | 4 | 44.4 | 6 | 66.7 |
| Relapse | 28 | 15 | 53.6 | N/A | N/A | 1 | 3.6 | 28 | 100 |

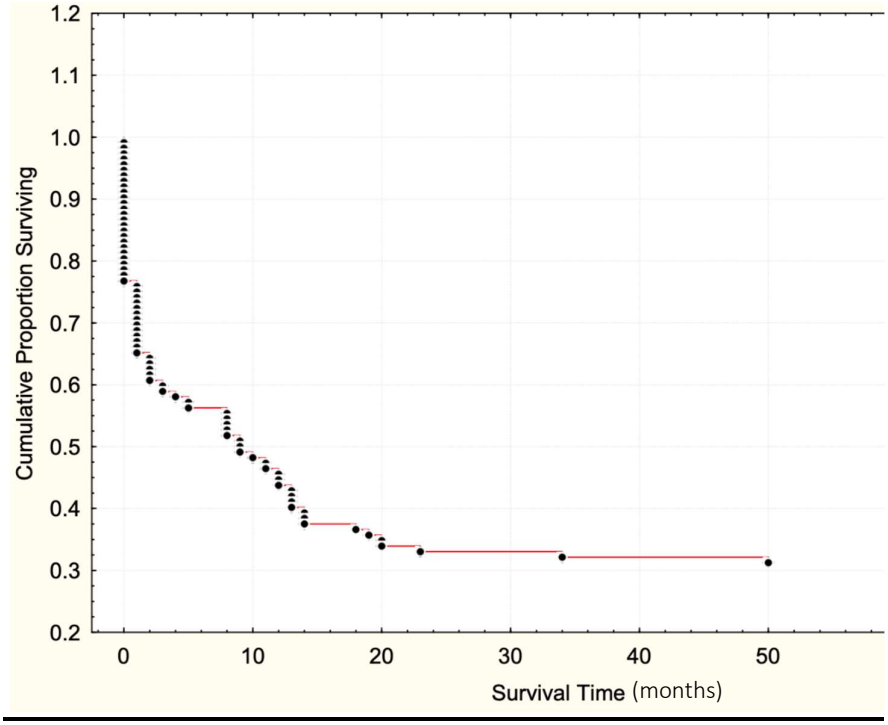


***Figure 4:*** *Kaplan Meier Curve.*

**Comparison between the two decades (Table 4)**

The twenty-year study period was divided into two periods (1998 to 2007 and 2008 to 2017). Comparing these two periods, there was a slight increase in the number of patients diagnosed with AML in the second ten years, 66, versus 53 in the first decade. The death rate was very similar (74% in the first decade and 68% in the second decade). Disease-related deaths declined from 57% to 39% and sepsis-related deaths increased from 19% to 29%, however this was found not to be statistically significant (p-value 0.09 and 0.3 respectively). There was a significant increase in the number of patients classified as M7 which is high risk and a decrease in M2, which is low risk (p-value 0.01 and 0.04 respectively).

The five-year survival did not show any significant difference with 16/53 (30%) surviving at least five years from diagnosis in the first decade and 22/66 (33%) in the second decade.

***Table 4:*** *Comparison between two decades*

| | 1998 – 2007 | | 2008 – 2017 | | Total | | P-values |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | |
| Total | 53 | 44.5 | 66 | 55.5 | 119 | 100 | |
| Outcome | | | | | | | |
| Deaths | 39 | 73.6 | 45 | 68.2 | 84 | 70.6 | 0.65 |
| 5-year Survival | 16 | 30.2 | 22 | 33.3 | 38 | 31.9 | 0.86 |
| Disease-related deaths | 30 | 56.6 | 26 | 39.4 | 56 | 47.1 | 0.09 |
| Sepsis-related deaths | 10 | 18.9 | 19 | 28.8 | 29 | 24.4 | 0.29 |
| Relapse | 14 | 26.4 | 14 | 21.2 | 28 | 23.5 | 0.65 |
| Gender | | | | | | | |
| Male | 25 | 47.2 | 28 | 42.4 | 53 | 44.5 | 0.73 |
| Female | 28 | 52.8 | 38 | 57.6 | 66 | 55.5 | 0.73 |
| Age | | | | | | | |
| Infants (0 - 12 months) | 6 | 11.3 | 13 | 19.7 | 19 | 16 | 0.32 |
| Pre-schoolers (>1 - 5 yrs) | 16 | 30.2 | 13 | 19.7 | 29 | 24.4 | 0.26 |
| Young children (>5 - 10 yrs) | 17 | 32.1 | 27 | 40.9 | 44 | 37 | 0.42 |
| Older children (>10 - 13 yrs) | 11 | 20.8 | 9 | 13.6 | 20 | 16.8 | 0.43 |
| Teenagers (>13 - 18 yrs) | 3 | 5.7 | 4 | 6.1 | 7 | 5.9 | 1 |
| FAB | | | | | | | |
| M0 | 2 | 3.8 | 4 | 6.1 | 6 | 5 | 0.69 |
| M1 | 2 | 3.8 | 2 | 3 | 4 | 3.4 | 1 |
| M2 | 19 | 35.8 | 12 | 18.2 | 31 | 26.1 | 0.04 |
| M3 | 8 | 15.1 | 15 | 22.7 | 23 | 19.3 | 0.41 |
| M4 | 6 | 11.3 | 6 | 9 | 12 | 10.1 | 0.92 |
| M4eos | 0 | 0 | 1 | 1.5 | 1 | 0.8 | 1 |
| M5 | 13 | 24.5 | 11 | 16.7 | 24 | 20.2 | 0.40 |
| M6 | 0 | 0 | 2 | 3 | 2 | 1.7 | 0.50 |
| M7 | 0 | 0 | 9 | 13.6 | 9 | 7.6 | 0.01 |
| Other | 1 | 1.9 | 3 | 4.5 | 4 | 3.4 | 0.62 |
| Unknown | 2 | 3.8 | 1 | 1.5 | 3 | 2.5 | 0.58 |
| WHO Classification | | | | | | | |
| Genetic abnormalities | 28 | 52.8 | 39 | 59.1 | 67 | 56.3 | 0.61 |
| Myelodysplastic changes | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Therapy-related | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| NOS | 26 | 49.1 | 25 | 37.9 | 51 | 42.9 | 0.29 |
| Myeloid sarcoma | 1 | 1.9 | 2 | 3 | 3 | 2.5 | 1 |
| Risk Profiles | | | | | | | |
| Standard Risk | 24 | 45.3 | 26 | 39.4 | 50 | 42 | 0.64 |
| Intermediate Risk | 3 | 5.7 | 4 | 6.1 | 7 | 5.9 | 1 |
| High Risk | 23 | 43.4 | 31 | 47 | 54 | 45.4 | 0.83 |
| Unknown Risk | 3 | 5.7 | 5 | 7.6 | 8 | 6.7 | 0.73 |
| Infections during Treatment | 38 | 71.7 | 55 | 83.3 | 93 | 78.2 | 0.19 |

**Acute Promyelocytic Leukaemia (Table 5)**

Twenty-three (19%) patients were classified as having APL, of which 18 (78%) had t(15;17) confirmation and the other five were classified using the FAB Classification. Thirteen were male (57%) and nine (39%) were between the ages of five and 10 years old. All of them had normal anthropometry. Two (nine percent) were classified as high risk because of other cytogenetics or gene mutations. One (four percent) had CNS involvement at diagnosis, one (four percent) had hyperleukocytosis and nine (39%) had platelets <20 x $10^9$/L. All of them received ATRA (All-trans retinoic acid). A total of 16 (70%) died, of which one (four percent) was prior to treatment. Eleven (48%) died during treatment, 3 during induction and eight (72%) were post ADE induction. Of the eight that died after ADE, three (37.5%) were due to disease-related complications and the other five (62.5%) died from sepsis. The five-year survival for patients with APL was 30%. Three patients with APL (13%) went into complete remission after ADE, five (22%) had resistant disease, but eight patients did not have a bone marrow done post-ADE and therefore the remission status was recorded as unknown. Three relapsed (13%), all three died. All three patients who relapsed, died.

***Table 5:*** *Baseline characteristics Acute Promyelocytic Leukaemia*

| APL | N | % |
|---|---|---|
| Total | 23 | 100 |
| Gender | | |
| Male | 13 | 56.5 |
| Female | 10 | 43.5 |
| Age | | |
| Infants (0 - 12 months) | 1 | 4.3 |
| Pre-schoolers (>1 - 5 yrs) | 6 | 26.1 |
| Young children (>5 - 10 yrs) | 9 | 39.1 |
| Older children (>10 - 13 yrs) | 4 | 17.4 |
| Teenagers (>13 - 18 yrs) | 3 | 13 |
| Nutrition | | |
| Underweight (wt-for-age <-2) | 6 | 26.1 |
| Severely underweight (wt-for-age <-3) | 0 | 0 |
| Overweight (wt-for-age >+2) | 0 | 0 |
| Obese (wt-for-age >+3) | 0 | 0 |
| Weight Unknown | 3 | 13 |
| Risk Profile | | |
| Standard Risk | 19 | 82.6 |
| Intermediate Risk | 0 | 0 |
| High Risk | 3 | 13 |
| Cytogenetics | | |

| | | |
|---|---|---|
| t(15;17) | 18 | 78 |
| Complex karyotype | 1 | 4.3 |
| Other | 2 | 8.7 |
| Unknown/not done | 2 | 8.7 |
| Clinical Characteristics | | |
| Hepatomegaly | 12 | 52.2 |
| Bleeding diathesis | 20 | 87 |
| CNS Involvement | 1 | 4.3 |
| WCC ≥ 50 x 109/L | 4 | 17.4 |
| WCC ≥ 100 x 109/L | 1 | 4.3 |
| Platelets <20 x 109/L | 9 | 39.1 |
| Outcome after ADE | | |
| Complete Remission | 3 | 13 |
| Resistant Disease | 5 | 21.7 |
| Relapse | 3 | 13 |
| Disease-related deaths | 11 | 47.8 |
| Sepsis-related deaths | 5 | 21.7 |
| Outcome | | |
| Died prior to Treatment | 1 | 4.3 |
| Died during Treatment | 11 | 47.8 |
| Died after Treatment | 4 | 17.4 |
| Completed Treatment | 7 | 30.4 |
| Died | 16 | 69.6 |
| Disease-related deaths | 11 | 47.8 |
| Sepsis-related deaths | 5 | 21.7 |
| 5-year Survival | 7 | 30.4 |
| Completed Treatment & 5-yr Survival | 6 | 26.1 |

## Discussion

Our mortality rate was surprisingly high (71%), with a five-year overall survival of only 32%. AML outcome data from other LMIC vary considerably: a two-year event-free survival of 0% in Tanzania,[11] a seven-year overall survival of 33% in China,[6] a 23% – 54% overall survival in India[7,12] and a 51% five-year overall survival rate in Mexico.[13] Overall childhood leukaemia cancer survival in South Africa was found to be 48.8%[8], however no data is available for AML specifically. A large proportion of our patients died prior to treatment (12%) contributing to our overall poor survival. These deaths can hopefully be addressed by strengthening early diagnosis and referral pathways.

Our early death rate of 32% is extremely high, compared to the 4-5% observed in HIC.[6,10] Studies done in India and China were able to achieve similar early death rates as that of HIC, of less than five percent, and this was ascribed to good supportive care.[6,14] In a systematic review of paediatric AML outcomes in LMICs, van Weelderen[5] et al found similar early death rates (up to 57%), and a study done in Korea reported early death rates as high as 58%.[15]

We are fortunate at our institution to have a reliable source of blood products, with an onsite blood bank as well as a nine-bedded, intensivist led paediatric intensive care unit (PICU). It would therefore be expected that our supportive care and survival be somewhat better than other LMIC experiences. However, our patients are often triaged negatively in favour of other paediatric patients with perceived more favourable outcomes due to limited intensive care bed availability. In our cohort, only 13% were admitted to ICU, whereas almost a third of patients with AML in HIC will have an ICU stay during their treatment.[16] Refusal of ICU admission is largely due to severe resource constraints with the historical poor prognosis associated with AML contributing to the decision to deny these patients even if a bed is physically available. Although we did not collect data on children who were denied ICU, this has most probably affected our survival negatively as well.

Many of our early deaths are reflective of treatment related mortality (mainly sepsis related deaths), raising the question whether we should reconsider whether it is in the patients' best interest to subject them to such intense induction chemotherapy, without being able to provide the required supportive care. SIOP PODC (The International Society of Pediatric Oncology, Pediatric Oncology in Developing Countries) has recently released AML treatment

guidelines[17] and Srinivasan et al[18] presented their results of using oral metronomic chemotherapy as a bridge to intensive chemotherapy in identified high-risk individuals. Further work could explore these options for use in our centre, weighing up the risk of relapse with de-intensified chemotherapy.

Comparing relapse from other HIC, 30%,[10] and most LMIC, 30% – 45%,[15] our relapse rate of 24% were even slightly better. However, not all patients received a bone marrow aspiration and trephine (BMAT) after ADE (22 patients), most likely due to complications related to the toxicity of ADE, or the result of the BMAT was not known and therefore this number might not reflect the true relapse rate.

Poor prognostic features have been shown to include ages between 10 and 19 years old, extremes of weight, resistant disease and hyperleukocytosis of more than 100 x $10^9$/L. Complete remission is also less likely in patients who are male, have a platelet count of <20 x $10^9$/L, a hepatomegaly at diagnosis and classified as FAB M5.[19,20] This is consistent with what we have found in our patient population showing high death rates and fewer patients obtaining complete remission when these factors were present.

Our centre is privileged to have access to excellent diagnostics including cytogenetics and molecular testing, and more recently next generation sequencing, with the ability to comprehensively classify and therefore risk stratify AML patients as well as to detect MRD. The number of patients who were classified as standard risk (42%) were comparable with that of HIC (30% – 40%),[20,21] but slightly higher than that of low-income countries (23% – 28%).[3,7] Our high-risk group (45%) was almost double that of HIC (20% to 24%) and even higher compared to low-income countries (12% – 18%).[3,7] We had a higher prevalence of high-risk FAB classes M5 (20%) compared with 16% in other LMIC, as well as M7 (eight percent vs two percent respectively). Less patients were classified as M2, (26%) which is standard risk, in comparison to other studies (43%).[2,22] This distribution of subtypes may contribute to our poor survival. Cytogenetic and molecular comparisons were not possible as data capturing stretched over a 20-year period during which the laboratory capabilities evolved. Further detailed analysis of disease biology in our patient population is warranted, and may in itself assist to explain the poorer outcomes observed.

Another concerning finding, is that our infection rate during treatment as well as sepsis-related death rate is high. It actually worsened in the last decade (although not statistically significant), compared to the first decade. One would have anticipated improved infection control over time, but perhaps with the rapid turnover of junior doctors and nurses rotating through the wards, the high stress environment and increased patient load might have resulted in worsened infection control practices. Furthermore, the deterioration in physical infrastructure has created an environment for infectious disease to flourish. Another possibility is an increase in multi-drug resistant organisms. Unfortunately, we did not capture the sensitivity of the culture proven infections. The increased sepsis-related deaths seen in the second decade resulted in a relative decrease in disease-related deaths. Culture negative septic episodes were not included in the definition of a septic episode and therefore these rates are most likely still an underestimate.

APL accounts for 3 to 10% of AML.[22] However, in our study population 19% were found to have APL. This subtype of AML has been associated with favourable outcomes with a survival rate of >70% across the world and in some regions an overall survival rate as high as 95%.[23] However, this number is thought to be an overestimate as patients who died prior to treatment were not included. An overall survival rate of 67% were reported in Brazil, a LMIC, more comparable to out setting.[24] Comparing these figures with our population, our five-year survival rate was found to be only 30%. Surprisingly, most of the deaths were due to disease-related complications (69%), however the septic deaths are still relatively high at 31%. Majority of deaths were observed just after the first induction, ADE, in keeping with the figures observed overall. This might indicate that this induction is too toxic, leading to more deaths than remission. Whilst APL really should be considered as a separate entity from other AML's we wanted to look specifically at this subgroup as there is significant room for improvement. Perhaps changing our protocol to a less intensive induction would lead to improved outcomes. We again need to strengthen early recognition, referral and ATRA initiation. For this subtype of AML, our efforts should be directed at improving overall supportive care in our environment.

**Strengths**

This study is the first review of paediatric AML at CHBAH and sets a benchmark for further quality improvement and comparison between centres (both public and private). We also included patients who were referred to our centre and demised prior to treatment initiation.

## Limitations

Our sample size was limited due to the rarity of the disease and the study site was limited to one hospital. We may have missed many teenagers who were treated by the adult haematology services, as it is not standard practice to refer all teenage patients to the paediatric oncology unit. We have a large number of patients who abandoned treatment, however little information exists on the reasons for abandonment and attempts to contact the families were in vain. The diagnostic capabilities of the lab were not uniform throughout the study period and therefore the FAB classification was used to risk stratify more often. Some records were incomplete, where files could not be found with only enough information to include them in the study.

## Conclusion

Survival of AML patients have increased significantly in HIC. Mostly due to improved supportive care, intensified risk-stratified chemotherapy, minimal-residual disease monitoring and stem cell transplantation. However, our survival is extremely poor with sepsis rates increasing. Induction with ADE has also proved to be most toxic. We are privileged in South Africa to have world class diagnostic capabilities and blood product availability, however this has not translated into survival advantage. We have significant limitations in access to newer chemotherapeutic agents, ICU care and HSCT and this affects overall survival. More studies would need to be conducted in our country including other paediatric oncology units as well as the private healthcare sector in order to better understand the outcomes and prognosis of AML in our setting as well as to an enhanced understanding of the pathways to care and factors contributing to treatment abandonment. This data will be used to guide strategies to improve survival of paediatric AML in our setting. Targeting early mortality, infection control and children with APL have the potential for significant benefit.

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**Author contributions**

Dr M Bassingthwaighte proposed the topic and Dr R de Jager designed the study, collected the data, analysed the data and wrote the final report under the supervision of Dr M Bassingthwaighte for the purpose of an MMed degree.

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**Data availability Statement**

The data supporting the findings of this research is available upon request from the authors.

Corresponding author: Dr RL de Jager: leonie.dj@gmail.com

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Rika Leonora de Jager

## HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

## CLEARANCE CERTIFICATE NO. M190324

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|---|---|
| **NAME: (Principal Investigator)** | Dr Rika Leonora de Jager |
| **DEPARTMENT:** | Health Sciences<br>Chris Hani Baragwanath Academic Hospital<br>Paediatric and Haematology Oncology Unit |
| **PROJECT TITLE:** | A retrospective review of paediatric acute myeloid leukemia at Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa |
| **DATE CONSIDERED:** | 29/03/2019 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Mairi Bassingthwaighte |
| **APPROVED BY:** | Dr CB Penny, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 05/09/2019 |

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

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Principal Investigator Signature Date

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A Retrospective review of paediatric acute myeloid leukaemia at Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa Abstract Background and Aims: Survival gains in paediatric acute myeloid leukaemia (AML) in high- income countries (HIC) have not been mirrored in low- and middle-income countries (LMIC). This study aimed to determine the disease spectrum, outcome and complications of paediatric AML in a resource constrained oncological service in Johannesburg, South Africa. Methods: From 1998 to 2017, the clinical details, treatment, outcome and complications of all paediatric patients with AML were analysed. Treatment was according to the Berlin-Frankfurt- Munster (BFM) AML 1998 protocol. Results: Over the 20-year study period 119 children, with a mean age of seven years, were diagnosed with AML. Fifty (42%) were classified as standard risk and 54 (45%) as high risk. Included in the cohort, were 23 patients diagnosed with Acute Promyelocytic Leukaemia (APL). Eighty-four (71%) patients died: 55 (65%) deaths were due to disease-related causes and 29 (35%) were due to sepsis. Forty-one (49%) of the deaths had occurred by the end of first induction. Infections during treatment were found in 93 (78%) patients and sepsis-related deaths