ACUTE MYELOID LEUKEMIA AT MUHIMBILI NATIONAL HOSPITAL: CLINICAL FEATURES, LABORATORY CHARACTERISTICS AND SURVIVAL OUTCOME

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ACUTE MYELOID LEUKEMIA AT MUHIMBILI NATIONAL HOSPITAL: CLINICAL FEATURES, LABORATORY CHARACTERISTICS AND SURVIVAL OUTCOME

By

Michelle Munroe

A Dissertation Submitted in (Partial) Fulfilment of the Requirements for the Degree of Master of Medicine (Hematology and Blood Transfusion) at

Muhimbili University of Health and Allied Sciences

October, 2024

CERTIFICATION

The undersigned certifies that they have read and hereby recommend for examination by the Muhimbili University of Health and Allied Sciences a dissertation entitled: *'**Acute Myeloid Leukemia at Muhimbili National Hospital: Clinical features, Laboratory Characteristics and Survival Outcome',*** in (partial) fulfillment of the requirement for the degree of Master of Medicine (Hematology and Blood Transfusion) of Muhimbili University of Health Allied Sciences.

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DECLARATION AND COPYRIGHT

I, **Michelle Munroe** hereby declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature..... Date.....

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I would like to extend my heartfelt gratitude to God, who has guided and supported me throughout this journey. His blessings and wisdom have been instrumental in my success.

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I would also like to acknowledge the unwavering support of my family, particularly my husband and children, who have been my rock throughout this process. Their love, patience, and understanding have been a constant source of strength and motivation, and I am deeply grateful for their presence in my life.

DEDICATION

For my beloved father, Thomas Theophilus Munroe and my dear mother Andrena Munroe.

ABSTRACT

Background: Acute myeloid leukemia is a blood cancer characterized by clonal expansion of immature blast cells in the peripheral blood and bone marrow, resulting in ineffective erythropoiesis and bone marrow failure. Chemotherapy is the mainstay of treatment, with bone marrow transplant reserved for patients with an intermediate risk or a high-risk disease. Nevertheless, the majority of AML patients who receive intensive chemotherapy and attain complete remission eventually relapse. Allogeneic stem cell transplant remains an essential treatment option in patients with good performance status. In the absence of timely treatment, AML has a rapid progression rate. Chemotherapy treatment for AML is available in Tanzania, but not always accessible to all patients. Little is known about the survival outcomes of patients with AML in Tanzania.

Aim of the study: To determine the clinical features, laboratory characteristics, and survival outcomes of patients with Acute myeloid leukemia treated with different regimens in Tanzania.

Materials and methods: This was a retrospective cohort analysis that included all patients with a confirmed diagnosis of AML by bone marrow aspiration from March 2018 to December 2023. Data was acquired from patient files and the electronic hospital record system. SPSS version 21 was used for data analysis. Descriptive statistics like percentage and mean were employed to describe the patients' demographic, clinical, and laboratory characteristics. The survival outcome was determined via the Kaplan-Meier method. Cox proportional hazards models were used to analyze survival results for patients with acute myeloid leukemia, identifying predictors of survival and estimating the correlation between each variable and survival outcomes. A p-value of <0.05 was considered significant.

Results: The prevalence of AML among all acute leukemia cases at MNH was 68% (n =112). Majority of the patients were females (60.7%), uninsured and had de novo AML. The mean age was 47.2 years (SD = 18.5). Most of the patients presented with symptoms of anemia (98.2%) and fever (79.5%). The median survival time was 81 days with a one-year overall survival of 15.2%. There was increased hazard of mortality for patients who resided outside of Dar es

Salaam (74% (aHR: 1.74, 95% CI: 1.15-2.64, p = 0.008) and those whose management constituted supportive treatment alone (aHR: 0.61, 95% CI: 0.40-0.93, p = 0.022).

Conclusions: Majority of the patients diagnosed with AML received palliative care and not standard of care. The survival outcome of AML in Tanzania is low.

Limitations: Due to the limited number of patients on LD cytarabine with venetoclax, we were unable to compare survival outcomes of patients on LD cytarabine with venetoclax and those on LD cytarabine alone

Recommendations: Patients should receive intensive chemotherapy which is deemed standard of care. We also consider the need for future prospective studies to be conducted on patients with AML receiving different treatment regimens, strong emphasis should be placed on the need for risk stratifying patients with AML inclusive of counselling patients for the need of molecular studies and the need for recording performance status (ECOG) in patients' files.

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LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
AML	Acute myeloblastic leukemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukemia
ATO	Arsenic trioxide
ATRA	All trans retinoic acid
BMA	Bone marrow aspiration
CBC	Complete blood count
CD	Cluster of differentiation
CNS	Central nervous system
CR	Complete response
DIC	Disseminated intravascular coagulation
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukemia Net
FAB	French American British
GO	Gemtuzumab Ozogomycin
HCT	Hematopoietic stem cell transplant
HMA	Hypomethylating agent
IQR	Inter quartile range
MNH	Muhimbili National Hospital
MRD	Minimum residual disease
NSSG	Network Site-Specific Group
OS	Overall survival
UK ALL	United Kingdom Acute Lymphoblastic Leukemia protocol

DEFINITION OF KEY TERMS

Survival outcome: refers to the chance of recovery or the percentage of people who will be alive at a certain time after the diagnosis of non-M3 AML is made (1).

Overall survival: the percentage of people with non-M3 AML who are still alive after 3 months, 6 months, 9 nine months, and one year, regardless of the cause of death (1).

1.0 INTRODUCTION

1.1 Background

Acute Myeloid Leukemia (AML) results from a malignant transformation and uncontrolled proliferation of an abnormally differentiated myeloid progenitor cell, which results in high circulating numbers of immature blood cells and replacement of normal bone marrow by malignant cells.

According to the American Cancer Society, "AML accounts for 11,310 deaths yearly". In the United States, there are around 20,000 cases of AML every year. The average age at the time of diagnosis is around 65 years (2). On the other hand, in the United Kingdom, more than 3000 persons are diagnosed yearly with AML and 42% of the cases are diagnosed in persons older than 75 years (3). Previous studies suggest that 50% of acute leukemia in Africa is AML, including a study of childhood malignancy from Nigeria in the 1980s. AML is reported in 20–25% of acute leukemia patients in more recent data from African hospital cancer registries(4). Leukemia was the 10th most prevalent cancer type in sub-Saharan Africa in 2018, with an estimated 20,900 new cases and 17,600 deaths. Males are somewhat more likely than females to develop leukemia, and around one-fourth of cases were diagnosed in children under the age of five (5). Data published in Africa from a study done in South Eastern Nigeria by Ugwu et al reported an incidence of 4.4% which is lower than that observed in the US and UK (6). The median age at diagnosis in Africa has also been reported to be lower. For instance, a study done in Western Kenya at Moi Teaching and Referral Hospital reported the median age of diagnosis to be 40 years old (7). A study done on Hematological malignancies in Tanzania revealed that AML represented 7.1% of hematological malignancies and the median age at diagnosis was 35 (8).

Based on the French–American–British (FAB) classification (9), the disease is confirmed by the presence of at least 20% primitive 'blast' cells in the bone marrow. The FAB morphological classification was designed in the 70s and was used as a dictionary for the morphological classification of AML into subtypes. In recent years, the FAB classification has been superseded by the revised scheme devised under the auspices of the WHO, which recognizes accumulating

knowledge of cytogenetic and molecular characteristics. The most recent WHO classification of hematologic neoplasia was done in 2022. Morphological features are becoming less mentioned with each revision of the WHO classification, while genetic factors are becoming more significant (10). With the recent classification for hematologic neoplasms, AML is divided into two families: AML defined by differentiation and AML determined by specifying genetic abnormalities. Most cases of AML with recognizable genetic abnormalities can be identified with 20% or fewer blasts (11)

Patients can present with symptoms and signs suggestive of anemia (pallor, weakness, headache), neutropenia (fever, infections) and thrombocytopenia (bleeding tendencies). The presentation is often during a short period which can range from a few days to a few months (12). Diagnosis of AML includes a complete blood count, peripheral blood smear, bone marrow examination, histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies. Auer rods, which are pathognomonic for AML are formed when myeloperoxidase-rich granules crystallize and form linear azurophilic inclusions in the cytoplasm of blast cells. Classifying acute myeloid leukemia requires the detection of particular immunophenotypic markers, such as CD13, CD33, CD34, and CD117 (13)

Various recurring translocations have been identified in AML. The identification of the t(15;17) translocation is important for diagnosing APL. Such a translocation generates the PML-RARA fusion gene, which has prognostic implications and offers specific treatment options with ATO and ATRA. Additionally, various recurrent gene mutations have been identified in AML such as mutations in the NPM1, CEBPA, RUNX1, DNMT3a, FLT3, KRAS, NRAS, ASXL1, IDH1/IDH2, TET2, U2AF1, SRSF2, KMT2A, TP53, and WT1 genes. Identification of any of these mutations may be important for the diagnosis, prognosis, and treatment of AML. For example, the identification of FLT3 mutations suggests that the disease course may be unfavorable. In the meantime, it may be possible to offer specific treatments using FLT3 inhibitors such as midostaurin (14).

The current standard treatment for AML is chemotherapy. Induction and consolidation (post-remission therapy) are the two basic phases of treatment. Cytarabine with an anthracycline medication, such as daunorubicin or idarubicin, makes up the most typical AML induction regimen. To achieve remission, induction therapy aims to eradicate as many cancer cells as possible. For induction therapy the 10+3 regimen and Triple IT is used for the pediatric population at MNH which was adapted from the UK ALL protocol. Daunorubicin at 50 mg/m2 via continuous infusion over 1 hour on days 1,3,5 with cytarabine 100 mg/m2 twice daily via continuous infusion for 30 minutes on days 1 through 10 are used. Triple IT comprises of methotrexate, cytarabine and hydrocortisone; they are given on day 1(the dose is age-adjusted). The total duration of therapy is 4 cycles and each cycle lasts for 28 days or until the count has recovered (whichever is longer). Induction chemotherapy is not routinely done for adult patients at MNH. The majority of adult patients at MNH receive low-dose cytarabine with the intent to palliate and less than a handful of adult patients with AML underwent induction therapy. About 6 patients underwent induction chemotherapy and they did not survive. Though these drugs are available in Tanzania most adult patients are placed on palliative care due to affordability and lack of active supportive treatment. Supportive treatment includes isolation in designated rooms to prevent infections, prompt transfusion of blood products, and antibiotics. With the lack of adequate and continuous supportive care, a palliative regimen seems to be the best choice for adult patients with AML at MNH since it can guarantee some months of survival compared to intense induction regimens which can lead to a shorter survival time when active supportive care is not guaranteed. Conducting a study on survival outcomes for acute myeloid leukemia at the main referral hospital in Tanzania, is crucial for several reasons inclusive of Centralized Patient Data, Comprehensive Patient Population, Access to Specialized Care and Comparison with Global Standards By evaluating survival outcomes at a major referral center, local data can be compared with international standards and identify gaps in care. This benchmarking can inform policy changes and resource allocation to improve AML treatment in Tanzania. : Findings from the study can contribute to the global understanding of AML in low-resource settings, highlighting unique challenges and potential solutions that can be applied in similar contexts across Africa and other developing regions. Conducting a survival outcome study on AML at Tanzania's main referral hospital is essential for improving understanding, treatment, and

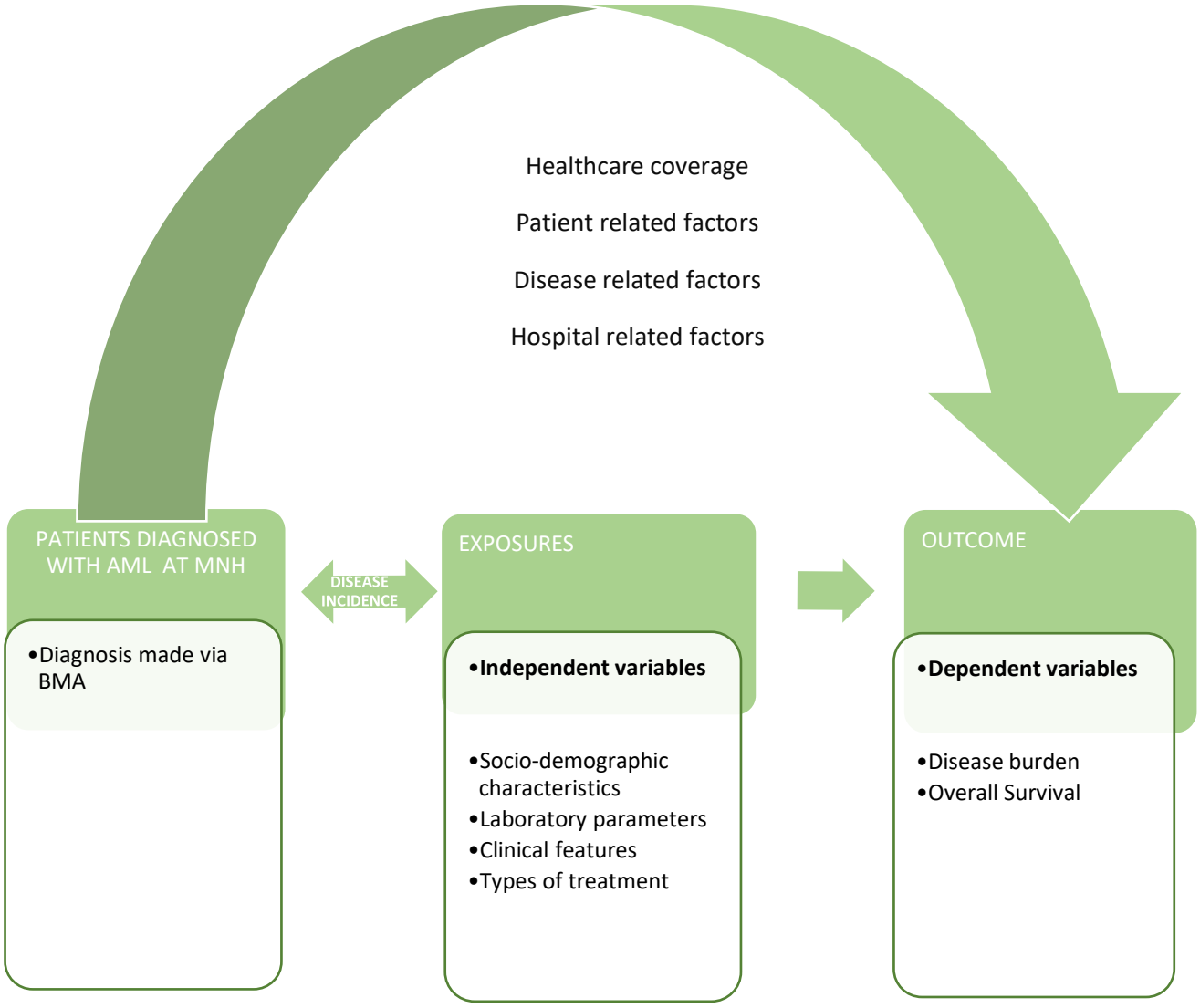
outcomes of this serious condition within the local context, while also contributing to broader global health knowledge. This study aims to portray relevant data that can be used to develop treatment protocols specific to the people of Tanzania.

1.2 Problem Statement

Acute myeloid leukemia is the most frequent type of leukemia in the adult population. Globally data exists on the survival outcome of AML, however, local data is not available. Patients are treated with the intent of palliation regardless of age, co-morbidities and performance status which is not standard treatment. Management of patients with AML is sub-optimal based on global standards. Consideration for optimal management is needed because with standard treatment remission can be achieved. To initiate changes in the management of patients we need to determine survival outcomes and use this to build a case for initiating different treatment regimens that have been observed to perform better. To make any progress towards improving survival, we first need to know the survival outcome. Furthermore, no database exists with the clinical and laboratory characteristics of patients with acute myeloid leukemia. A starting point with the same is needed for a better management approach.

1.3 Conceptual framework

Figure 1: Conceptual framework



Healthcare coverage can be influenced by various factors related to the patient, disease, and hospital. Patient-related factors include demographic variables such as age, ethnicity and gender, as well as the patient's understanding of the illness and treatment. Disease-related factors encompass the severity of the disease, symptoms, and comorbidities. The World Health Organization has identified five sets of factors that affect patients' adherence to therapy: socio-economic, healthcare team and system-related, condition-related, therapy-related, and patient-related factors. Studies have shown that age, sex, and geographical location can influence AML survival outcomes. The bone marrow and blood cell count, as well as the presence of specific gene mutations, can impact AML survival. Advances in AML treatment, such as more aggressive chemotherapeutic regimens, bone marrow transplantation, and subtype-directed therapies, have led to improved survival, the choice of treatment and the intensity of therapy can also influence survival outcomes.

1.4 Rationale

It is crucial to undertake this study in Tanzania as it will be the first study to provide data on our patient's clinical and laboratory characteristics, as well as their survival based on different treatment regimens. From studies, done on other cancer types, it is evident that global statistics on survival outcomes vary. It is therefore important that we understand the Tanzanian context; elements like genetics, lifestyle, and access to healthcare may result in variations in the prevalence of AML as well as the survival outcome.

An overview of the epidemiology, clinical, and laboratory aspects will give a larger picture of the impact of the disease and the need for more resources to be dedicated to its early diagnosis, risk stratification, and appropriate treatment. The survival outcome in relation to the treatment regimen will allow a more standardized and clearer approach for better and well-suited treatment regimens.

1.5 Research Questions

1. What are the clinical features of patients with Acute myeloid leukemia in Tanzania?
2. What are the laboratory characteristics of patients with Acute myeloid leukemia in Tanzania?
3. What is the survival outcome among patients treated for Acute myeloid leukemia with different treatment regimes in Tanzania?

1.6 Objectives

1.6.1 Broad Objective

To determine the clinical features, laboratory characteristics, and survival outcomes of patients with Acute myeloid leukemia in Tanzania.

1.6.2 Specific Objectives

1. To describe the clinical features of patients with Acute myeloid leukemia in Tanzania
2. To describe the laboratory characteristics of patients with Acute myeloid leukemia in Tanzania
3. To determine the survival outcomes of patients treated for AML in Tanzania

2.0 LITERATURE REVIEW

2.1 Clinical and laboratory characteristics of patients with AML

The most frequent symptoms are weakness and fatigue. Pallor, dyspnea on exertion, palpitations, and an overall decline in well-being have all been reported (15). About 15% to 20% of patients have a fever, which can be caused by bacterial, fungal, or, less frequently, viral infections. It can also be a result of the leukemic burden on tissues and organs. Other severe symptoms related to decreased platelet counts that occur less commonly are gastrointestinal or genitourinary tract or intracranial bleeding. Disseminated intravascular coagulation and other abnormal bleeding patterns can be present, especially in the M3 subtypes (APL) (15,16). A study in the USA revealed that exhaustion was most frequently reported (95.7%), followed by bruises and weakness (both 78.3%). A similar study in Japan showed that nausea was most frequently reported (94.4%), followed by fatigue and headache (both 88.9%) (16).

It is also possible to see malignant cell infiltration into the skin, gums, and other mucosal areas. In half of AML patients, splenomegaly is present, while lymph node enlargement is uncommon except in the monocytic type (17),18). The most typical skin conditions are pustules or other mild pyogenic infections of small cuts or wounds. Major infections, including sinusitis, pneumonia, pyelonephritis, and meningitis, are infrequent when the disease first manifests, in part because absolute neutrophil levels below 0.5 x 10^9/L are unusual before chemotherapy begins. Following chemotherapy, severe bacterial, fungal, or viral infections are increasingly common as neutropenia and monocytopenia worsen (19).

The initial steps in the laboratory diagnosis of leukemia are the CBC and inspection of a peripheral blood smear. Variable blood cell counts are seen in AML patients.

WBC might be raised, reduced, or normal. Less than 20% of the time, it is markedly raised (more than 100 x 10^9/L cells). On the other hand, at the time of diagnosis, approximately 50% of patients have a WBC of less than 5 x 10^9/L and an absolute neutrophil count of less than 1.0 x 10^9/L.17 Blasts are typically seen on the peripheral smear in leukopenic patients, but their numbers may be sparse and difficult to find (20).

Anemia is a very frequent condition brought on by an insufficient generation of healthy red blood cells. Typically, the reticulocyte count is normal or declining. Nearly invariably, thrombocytopenia—which can be severe—is present at the time of diagnosis. It's possible to also see large and agranular platelets. A hypercellular bone marrow with 20% to 90% leukemic blasts at diagnosis or during relapse is the defining characteristic of acute leukemia (19) Other laboratory findings may include hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and elevated lactic dehydrogenase. These findings indicate a tumor lysis syndrome. Elevated serum levels of hepatic transaminases and/or creatinine and pseudo hypoglycemia may also be present.

2.2 Treatment and survival outcome

With current standard protocols, after the diagnosis of AML patients are categorized as fit or less fit(21). The less fit patients are typically treated with less intensive regimens such as Hypomethylating agents (HMA), supportive care, or a clinical trial. Fit patients undergo European Leukemia Net (ELN) risk stratification to determine whether the risk is favorable, intermediate, or unfavorable. Favorable cases are treated with induction plus consolidation chemotherapy, intermediate cases are given consolidation chemotherapy or HCT transplant and unfavorable cases have a better outcome with allogeneic HCT (22). The "7 plus 3" regimen, which combines daunorubicin at 45 to 90 mg/m2 on days 1 through 3, with cytarabine 100 mg/m2 daily via continuous infusion on days 1 through 7 is used for adult patients under the NSSG protocol. The "7 plus 3" regimen has been revised and updated to the "10 plus 3" regimen, where cytarabine is given for ten days instead of seven (23). At MNH low dose cytarabine is given following the NSSG Hematology protocols, however low dose cytarabine is indicated with the intent to palliate and not to cure.

Treatment of acute myeloid leukemia includes initial induction therapy and post-remission therapy. Induction therapy aims to achieve complete remission, if possible, without measurable residual disease. Regardless of the kind of induction therapy used, one Swedish trial found that patients who attained CR had increased survival (24). The patient's functional status (best assessed by performance status and comorbidities), biological disease status, and preferred initial induction therapy depend on each other. Cytotoxic chemotherapy with or without targeted

therapy and hypomethylating drugs with or without targeted therapy are two induction therapies for acute myeloid leukemia that are often used (25).

Up to 80% of patients with a favorable disease risk respond completely to this induction therapy, also known as 7+3, and 50 to 60% of patients with intermediate-risk respond completely (26). The outcomes in the favorable and intermediate risk groups have improved with the addition of several targeted drugs to traditional induction chemotherapy 7+3. A monoclonal antibody called gemtuzumab ozogomycin is directed against the protein CD-33, which is expressed in myeloid leukemia cells. In some studies, adding GO to regular chemotherapy increases overall survival and lowers the chance of illness recurrence in individuals with good disease or intermediate risk of disease. Benefits are more significant in favorable risk diseases than in intermediate risk diseases (27). Patients with FLT3 mutation had enhanced survival when midostaurin was added to conventional 7+3 chemotherapy, increasing it from 25 to 74 months on average (28).

Standard 7+3 chemotherapy still yields inadequate results for diseases with increased risk. Only approximately 40% of patients achieve a complete response (CR), and their average overall survival is 12 to 18 months. Nearly half of patients relapse even after allogeneic hematopoietic stem cell transplantation (HCT). In recent years, the association of venetoclax with hypomethylating agents significantly improved the outcome of newly diagnosed AML unfit for intensive chemotherapy and became the standard of care in this subgroup of patients.Venetoclax is an oral highly selective inhibitor of the anti-apoptotic protein BCL-2. In patients with unfavorable risk AML, BCL2 is hypothesized to mediate resistance to conventional therapy (29). Venetoclax was investigated in patients with adverse risk diseases in combination with hypomethylating drugs (decitabine and azacitidine). Results with venetoclax combined with hypomethylating medications were superior to results with hypomethylating agents alone, even in older patients, patients with insufficient cytogenetic characteristics, and patients with harmful molecular mutations (30). In these early investigations, the median overall survival was roughly 15 months. compared to the past median survival time of about 10 months with hypomethylating drugs alone, which is a significant improvement (31).

Remission is defined as the elimination of the leukemic cell population in the marrow as judged by microscopy and flow cytometry and the restitution of marrow hematopoiesis resulting in a normal or virtually normal white cell, hemoglobin, and platelet concentrations in the blood.

Treatment options for recurrence may include various chemotherapy regimens, allogeneic HCT transplantation, or other novel approaches (32).

In the USA for the decades 1980 to 1989, 1990 to 1999, 2000 to 2009, and 2010 to 2017, the overall 5-year survival rates for people with AML were 9%, 15%, 22%, and 28%, respectively. The 5-year survival rates were 24%, 41%, 52%, and 63% for patients between the ages of 15 and 39; 1%, 2%, 3%, and 5%, respectively, for patients above the age of 70. Even in the modern era, the four-week mortality rate among adults and elderly patients was surprisingly high (range, 20%-45%). Overall, survival increased across the years and was at its highest from 2010 to 2017. Except for patients over 70 years old, where the expected 5-year survival rate remained at 5% even after treatment, there was a notable improvement in survival across all age categories (33). The median survival for older patients (median age 78) with AML in the USA was two months in the untreated group *versus* six months in the treated group. In addition, in patients who received allogeneic hematopoietic cell transplantation, the median survival from diagnosis was 22 months (34).

The outcomes of AML have continued to be a serious problem in nations with limited resources. In Taiwan the median OS for patients younger than 65 was 18 months and for those older than 65 it was 5 months (35). According to Brazilian research, for individuals with AML who had extensive chemotherapy the median overall survival was 38.82 months. Furthermore, in 5 years, the overall survival rate was 39.4%; in 2 years it was 56.5%; 66.5% in one year, and; 74.9% in six months of follow-up (36). Based on a study conducted by Christopher Mwaniki Wanjiku et al from Kenya, the one-year survival outcome for patients with non-M3 AML was 7.9% and the median overall survival after diagnosis was 45 days(7). In Uganda, the one-year survival for AML was 16.5%, with a median survival time of 47 days (37).

A study on the outcome of childhood leukemia in Tanzania by E. Kirsten concluded that 84% of the patients with ALL and 35% with AML who underwent therapy had achieved complete remission. In addition, all patients with ALL had an estimated 2-year event-free survival of 33%; whereas for the patients with AML, it was 0% (38)

In a study done by Stabellini et al males had a higher frequency of AML than females, and their findings indicated the significance of mutational factors as well as the role that age, race, and treatment—including BMT, chemotherapy, hospital stays, and adherence to treatment—play in survival (39). A study done on factors affecting survival outcome by Baghban et al concluded that such factors included age at the time of diagnosis, WBC count, smoking, family history, LDH and AST levels (40) .

3.0 MATERIALS AND METHODS

3.1 Study design

This was a retrospective cohort study.

3.2 Study area

The study was conducted at the Muhimbili National Hospital (MNH). MNH has two facilities: Mloganzila in the Ubungo district and the main facility situated at Upanga in Ilala district. MNH is a national tertiary hospital that serves as a teaching facility for the Muhimbili University of Health and Allied Sciences (MUHAS. It can accommodate 1500 patients, with 1200 outpatients per day and 1000 admissions per week. The hematology patients are attended at both facilities. Eight hematologists, together with two hematology-trained nurses, serve at MNH. MNH Mloganzilla offers a hematology clinic every day of the week. MNH Upanga offers a coagulation clinic on Tuesdays and a General Hematology clinic on Fridays. Approximately 70 patients are attended at the General Hematology Clinic. MNH features a records management system that comprises both physical and electronic components. The Medical Records Department of the hospital is in charge of creating, maintaining, and managing these records. MNH compiles and keeps actual documents on paper. Patient charts, medical histories, and other pertinent information are included in these physical records. The Emergency Medicine Department of MNH installed and deployed the first EMR system, Jeeva, in 2015. This electronic system enables the digital storage, retrieval, and management of patient information such as demographic data, laboratory tests, imaging, and so on. The Jeeva system is accessible to staff of MNH and students of MUHAS who are provided with a user account and password. The physical records can be accessed from the Medical Records department by the staff and students with granted permission.

3.3 Study Population

The study population included all patients diagnosed with Acute leukemia by bone marrow aspiration morphology from March 2018 to December 2023 at the Muhimbili National Hospital

3.4 Study duration

The study was conducted for 3 months. The time frame was from January 2024 to March 2024.

3.5 Selection Criteria:

3.5.1 Inclusion criteria

a) Patients diagnosed with non-M3 Acute myeloid leukemia by bone marrow aspiration morphology from March 2018 to December 2023 via a bone marrow aspirate
b) All patients with age 18 years and above

3.5.2 Exclusion criteria

a) Patients with acute promyelocytic leukemia (M3 AML)
b) Patients with incomplete data insufficient to answer the research questions

3.6 Sample size and power calculation

A study from Uganda by Barbra Natukunda et al., which showed a one-year survival rate of 16.5%, was used to estimate the sample size.

Study Parameters

Incidence, population 16.5%

Incidence, study group 6.5%

Alpha 0.05

Beta 0.15

Power 0.85

Sample size-97

The estimated sample size was 97 patients, however all the patients diagnosed with AML from January 2018 to December 2023 were included in this study.

Power calculation

$$N = \frac{p_0 q_0 \left\{ z_{1-\alpha/2} + z_{1-\beta} \sqrt{\frac{p_1 q_1}{p_0 q_0}} \right\}^2}{(p_1 - p_0)^2}$$

$$q_0 = 1 - p_0$$

$$q_1 = 1 - p_1$$

$$N = \frac{0.165 * 0.835 \left\{ 1.96 + 1.04 \sqrt{\frac{0.065 * 0.935}{0.165 * 0.835}} \right\}^2}{(0.065 - 0.165)^2}$$

$$N = 97$$

Where:

p0 = proportion (incidence) of population

p1 = proportion (incidence) of the study group

N = sample size for the study group

α = probability of type I error (usually 0.05)

β = probability of type II error (usually 0.2)

z = critical Z value for a given α or β

3.7 Enrollment of Participants

Charts were recruited from the records management system of MNH Upanga. All patients with a confirmed BMA diagnosis of acute myeloid leukemia from March 2018 to December 2023 were enrolled in the study.

3.8 Variables

3.8.1 Independent variables

Socio-demographic characteristics

-age, gender, region, insurance status

Clinical features

-symptoms of anemia, fever, bleeding tendencies, lymphadenopathy, organomegaly, presence of co-morbidities

Laboratory parameters

-Total leucocyte count, differential leukocyte counts, hemoglobin level, platelet count, peripheral smear, FAB classification, bone marrow aspirate findings

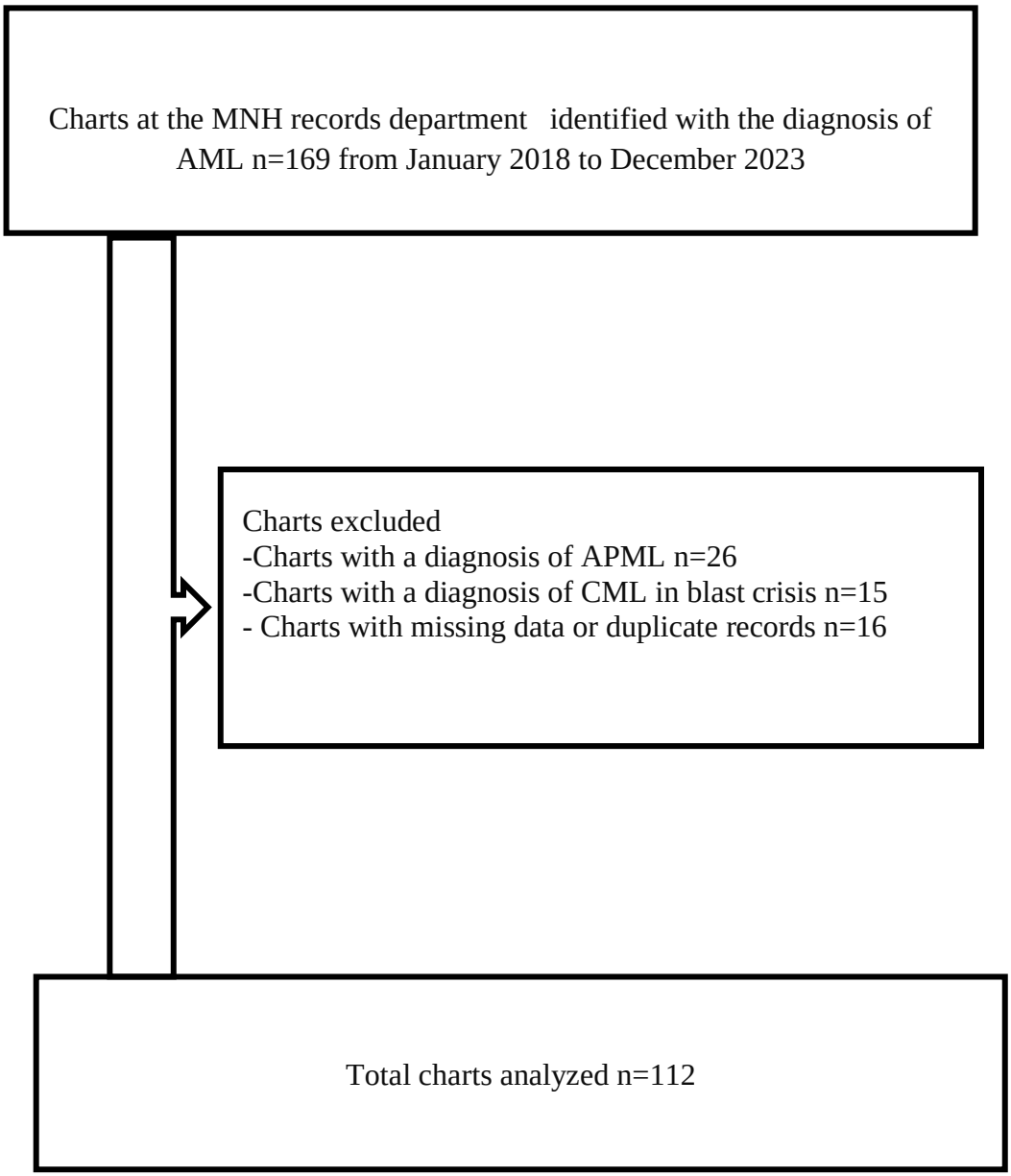
3.9 Dependent variable

-Survival outcome

3.10 Data Collection

Data was collected from the digital hospital record system (JEEVA) and files of patients on a predefined data collection sheet and then entered into a Microsoft Excel sheet. Details of the patients included treatment regimen, age, gender, insurance status, symptoms, presence of lymphadenopathy, presence of hepatosplenomegaly, baseline comorbidities, AML categories (de novo, myelodysplasia-related, myeloproliferative-related, therapy-related), bone marrow aspirate and peripheral blood smear findings. Patients with missing data were excluded from this study. The missing data from patient's files included those without bone marrow aspirate findings and those with conflicting bone marrow aspirate results. Phone calls were made to the relatives of the patients' to determine whether the patient was still being followed up at another institution or the patient had died.

Figure 2: Flow chart



3.11 Data analysis

After clinical and analytical data pertaining to individuals with AML was gathered from medical records, they were summarized using descriptive statistics like median, and standard deviation. STATA v16 was used for data analysis. The survival outcome was calculated using the Kaplan-Meier method. To evaluate the significance of the results, a p-value of 0.05 was be utilized. In addition to the Kaplan Meier method, the Cox proportional hazards model was be used to determine survival predictors and calculate the effect of covariates on survival. The Cox proportional hazards model was used to estimate hazard ratios and account for confounding variables, while the Kaplan-Meier method was used to estimate the survival function and compare survival curves between groups. Cox proportional hazards models was used to analyze survival results for patients with acute myeloid leukemia, identifying predictors of survival and estimating the correlation between each variable and survival outcomes. Additionally, estimation of the survival curves for various treatment regimens and residence using the Kaplan-Meier method was done.

3.12 Ethical clearance

Ethical clearance was obtained from the two primary bodies MUHAS IRB and MNH Research and Consultancy Bureau. Data was kept anonymous and was only used for this study by the researcher and the supervisors.

4.0 RESULTS

4. What are the clinical features of patients with Acute myeloid leukemia in Tanzania?
5. What are the laboratory characteristics of patients with Acute myeloid leukemia in Tanzania?
6. What is the survival outcome among patients treated for Acute myeloid leukemia with different treatment regimes in Tanzania?

4.1 Prevalence of acute myeloid leukemia, Social demographic and Clinical characteristics of the study participants

Initially 245 patients were identified with acute leukemia, the prevalence of acute myeloid leukemia among the patients diagnosed with acute leukemia at MNH from 2018 to 2023 was 68% (169/245) and the prevalence of ALL was 32% (78/245) (figure 3). Majority of participants with AML resided in Dar es Salaam, Tanga, Pwani and Zanzibar (figure 4).

The study comprised 112 individuals, 60.7% (68/112) female, with 23.4% (26/112) below 29 years, 27.0% (30/112) between 30 and 49 years, and 49.6% above 49 years, with a mean age of 47.2 years (SD = 18.5). Regarding residency, 53.6% lived in Dar es Salaam, while 46.4% resided outside the city. Only 27.7% (31/112) participants were insured. The majority of the patients had De novo AML, 92% (103/112) and 17.9% (20/112) of the patients had co-morbidities (Table 1).

The two most common presenting clinical features of the patients diagnosed with AML were symptoms of anemia, 98.2% (110/112) and fever 79.5% (89/112). Only 43.7% (49/112) of the patients presented with bleeding tendencies. Other presenting features such as bone pain and lymphadenopathy were represented by 16.1% (18/112) and organomegaly was present in 13.4% (15/112) (figure 5).

Figure 3: Prevalence of acute myeloid leukemia among patients diagnosed with acute leukemia

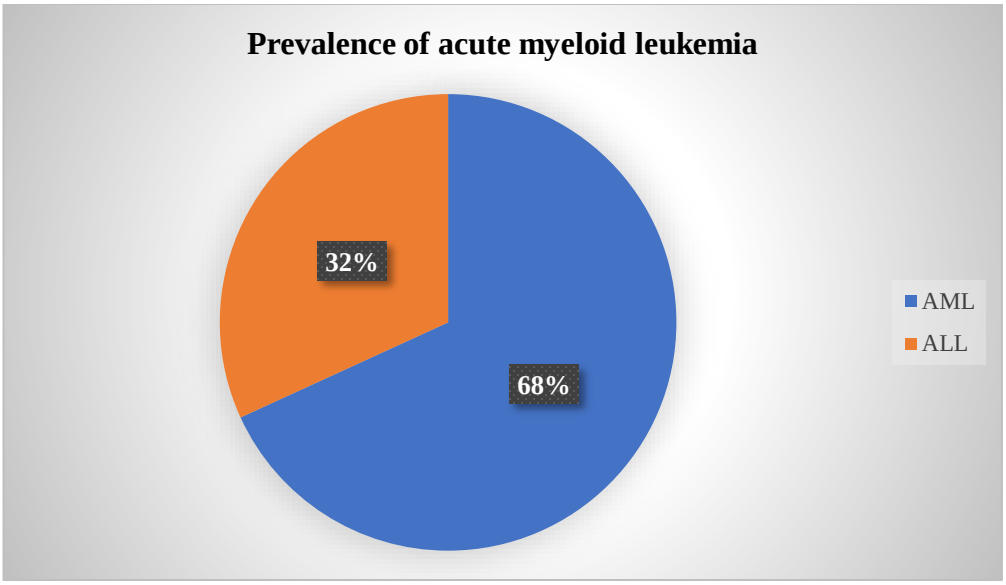


Figure 4: Regions of residence for patients with AML who attended MNH

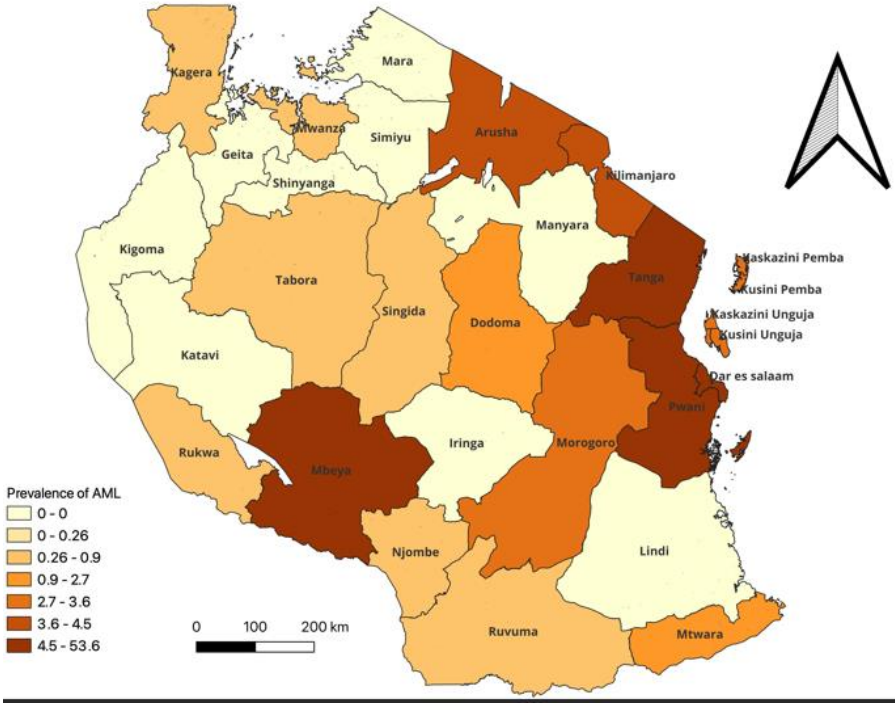
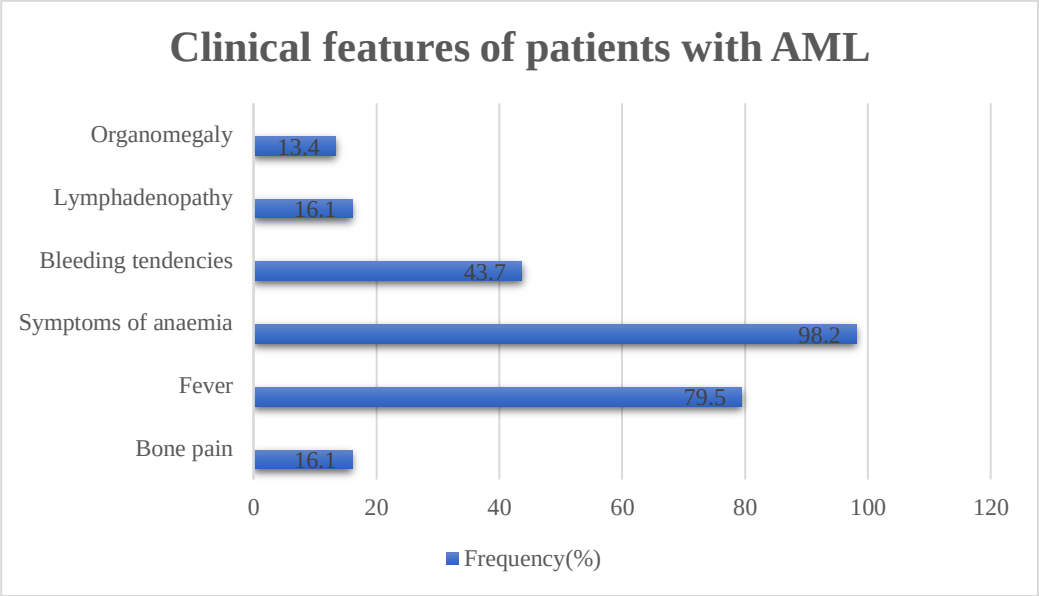


Table 1: Social demographic and clinical characteristics of the patients (n=112)

Variable	Frequency	Percentage
Sex		
Male	44	39.3
Female	68	60.7
Age group		
Below 29	26	23.4
30-49	30	27.0
Above 49	55	49.6
Mean SD for age		
	47.2	18.5
Place of residence		
Dar es Salaam	60	53.6
Outside Dar es Salaam	52	46.4
Insurance status		
Insured	31	27.7
Not insured	81	72.3
Comorbidities		
No	92	82.1
Yes	20	17.9
De novo AML		
No	8	7.1
Yes	103	92.0
Unspecified	1	0.9
Secondary AML		
No	103	92.0
Yes	8	7.1
Unspecified	1	0.9

Figure 5: Clinical features of patients with acute myeloid leukemia

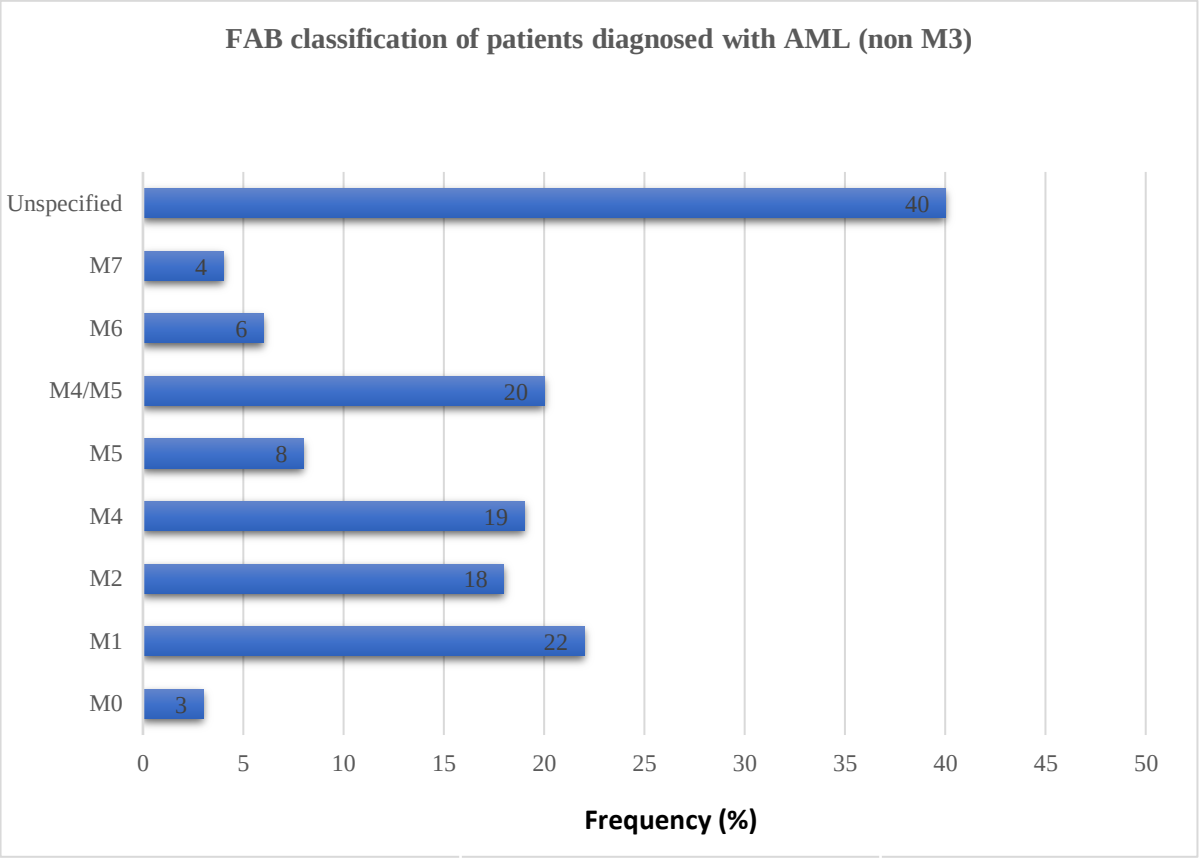


4.2 Laboratory characteristics of patients with AML

4.2.1 FAB classification of patients diagnosed with AML (n =112)

Utilizing the French-American-British (FAB) classification system, the distribution of subtypes was as follows: M1 accounted for 14.2% of cases, M2 for 10.7%, M4 for 9.9%, M5 for 6.2%, M4/M5 for 13.4%, M6 for 4.5%, M7 for 3.6%, and Unspecified cases made up the largest proportion at 35.7%. The cases referred to as unspecified were those which could not be grouped into the FAB classification by looking at the morphology alone. All of the cases classified utilizing the FAB classification system were based on bone marrow morphology without flow cytometry.

Figure 6: FAB classification of patients diagnosed with AML (n = 112)



4.3 Median Blood counts at diagnosis and after receiving the first and fourth treatment cycles

White Blood Cell (WBC) counts declined significantly ($p < 0.001$) after the first treatment cycle (median = 3.6, IQR = 1.8 - 15.2). Similarly, Absolute Neutrophil Count (ANC) showed significant variation ($p = 0.005$), decreasing (median = 1.8, IQR = 0.4 - 6.4) after the first cycle (median = 0.5, IQR = 0.1 - 1.6) and then increasing slightly after four cycles (median = 0.7, IQR = 0.2 - 2.0). Hemoglobin (HB) levels exhibited significant differences ($p < 0.001$), with higher levels after the first cycle (median = 7.4, IQR = 5.6 - 8.6), compared to levels at diagnosis (median = 6.1, IQR = 5.1 - 7.3), and a further increase after four cycles (median = 10.1, IQR = 8.9 - 11.6). Platelet counts also differed significantly ($p = 0.001$) among the time points, with a notable increase after the fourth treatment cycle (median = 197.0, IQR = 84.6 - 245.0), compared to levels at diagnosis (median = 35.6, IQR = 18.5 - 58.6) (Table 2).

Table 3 further demonstrates which time points were responsible for the observed statistically significant differences demonstrated in Table 2 above, through a pairwise comparison of laboratory values at the three time points. For WBC, there was a significant difference between the first cycle and at diagnosis (median difference: 3.91, $p < 0.01$), while the comparison between the other cycles was not statistically significant. The difference between the first cycle and at diagnosis for the ANC (median difference 3.04, p-value 0.007) was found to be statistically significant. For HB, pair-wise comparisons were significant between the first cycle and at diagnosis (median difference -2.71, p = 0.020) and between the fourth cycle and diagnosis (median difference -3.77, p value 0.004). Regarding platelet count, significant differences were observed between the fourth cycle and at diagnosis (mean difference: 3.62, $p < 0.001$), as well as between the first cycle and the fourth cycle (mean difference: 2.58, $p < 0.001$), whereas the difference between the first cycle and diagnosis was not statistically significant (mean difference: 25.55, $p = 0.029$).

Table 2: Median values and IQR for laboratory results

Variable	Stage			
	At diagnosis Median (IQR)	After 1st cycle Median (IQR)	After four cycle Median (IQR)	*p-value
WBC	14.9(5.5 – 51.3)	3.6(1.8 – 15.2)	4.3(2.8 – 5.6)	<0.001
ANC	1.8(0.4 – 6.4)	0.5(0.1 – 1.6)	0.7(0.2 – 2.0)	0.005
HB	6.1(5.1 – 7.3)	7.4(5.6 – 8.6)	10.1(8.9 – 11.6)	<0.001
Platelet	35.6(18.5 – 58.6)	45(20.5 – 82.8)	197.0(84.6 – 245.0)	0.001

***Kruskal Wallis**

Table 3: Pairwise comparison of median laboratory values

Pairwise comparison	Median difference	*p-value
WBC		
After 1st cycle – After 4 cycles	-0.65	1.000
After 1st cycle - At diagnosis	3.91	<0.001
After 4 cycles– At diagnosis	2.82	0.014
ANC		
After 1st cycle – After 4 cycles	0.11	1.000
After 1st cycle - At diagnosis	3.04	0.007
After 4 cycles– At diagnosis	1.58	0.346
HB		
After 1st cycle – After 4 cycles	2.16	0.092
After 1st cycle - At diagnosis	-2.71	0.020
After 4 cycles– At diagnosis	-3.77	0.004
Platelet		
After 1st cycle – After 4 cycles	2.58	0.029
After 1st cycle - At diagnosis	-1.61	0.324
After 4 cycles– At diagnosis	-3.62	<0.001

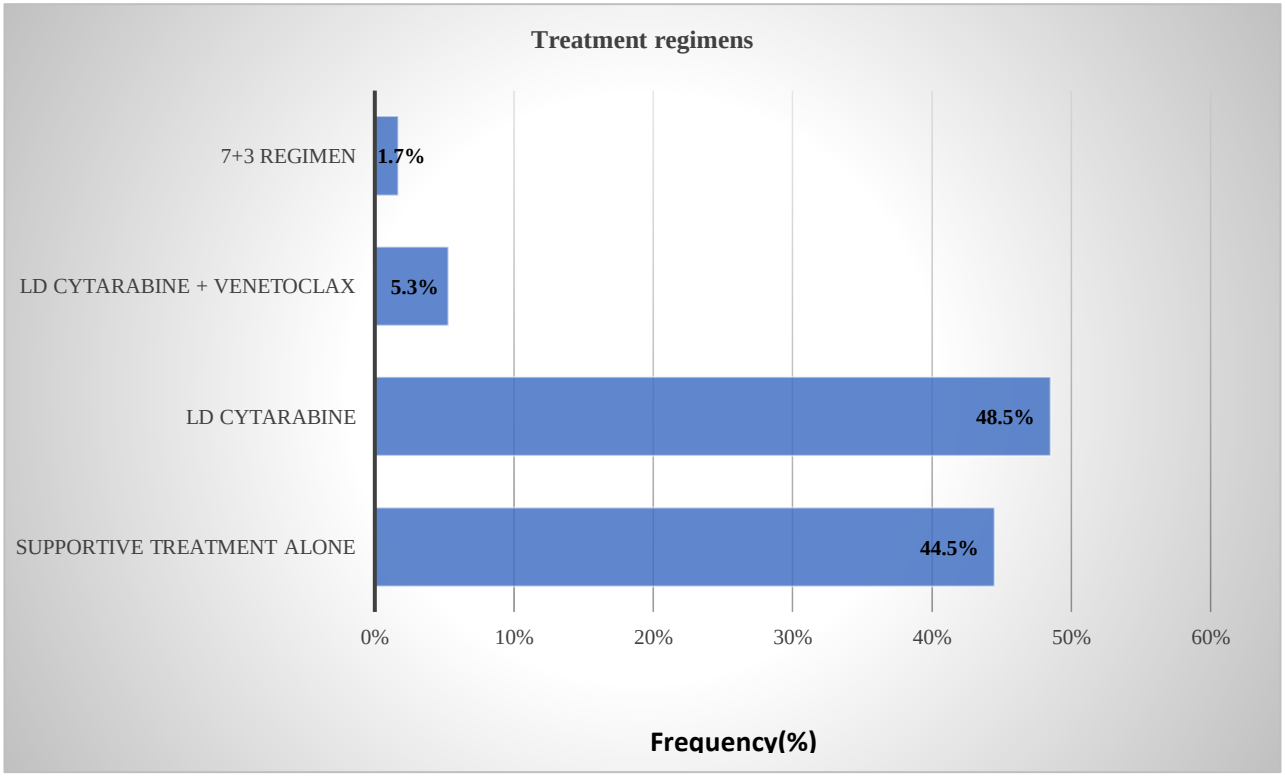
***Dunn test**

4.4 Treatment regimens used by patients with non-M3 AML at MNH and Survival outcomes of patients treated for acute myeloid leukemia with low-dose cytarabine or cytarabine with venetoclax

4.5 Treatment regimens used by patients with non-M3 AML at MNH

Only 1.7% (2/112) of the patients received standard of care, 5.3% (6/112) received LD cytarabine with venetoclax, 48.5% (54/112) received LD cytarabine and 44.5% (50/112) were on supportive treatment alone.

Figure 7: Treatments regimens used by patients with non-M3 AML



4.5.1 One-year Overall survival of non M3 acute myeloid leukemia patients

Within the initial 90 days following diagnosis, the survival probability is 42.0% (95% CI: 32.8-50.9), with a further decline to 24.1% (95% CI: 16.7-32.3) at 180 days. Subsequently, between 180-270 days, the survival rate drops to 17.9% (95% CI: 11.4-22.4), and after 365 days, only 17 patients were still alive resulting in a one-year overall survival of 15.2% (Table 4) (Figure 8). The five-year OS for non-M3 AML was 5.4% (Figure 9).

Figure 8: Kaplan Meier curve showing overall survival of non-M3 acute myeloid leukemia patients in one year

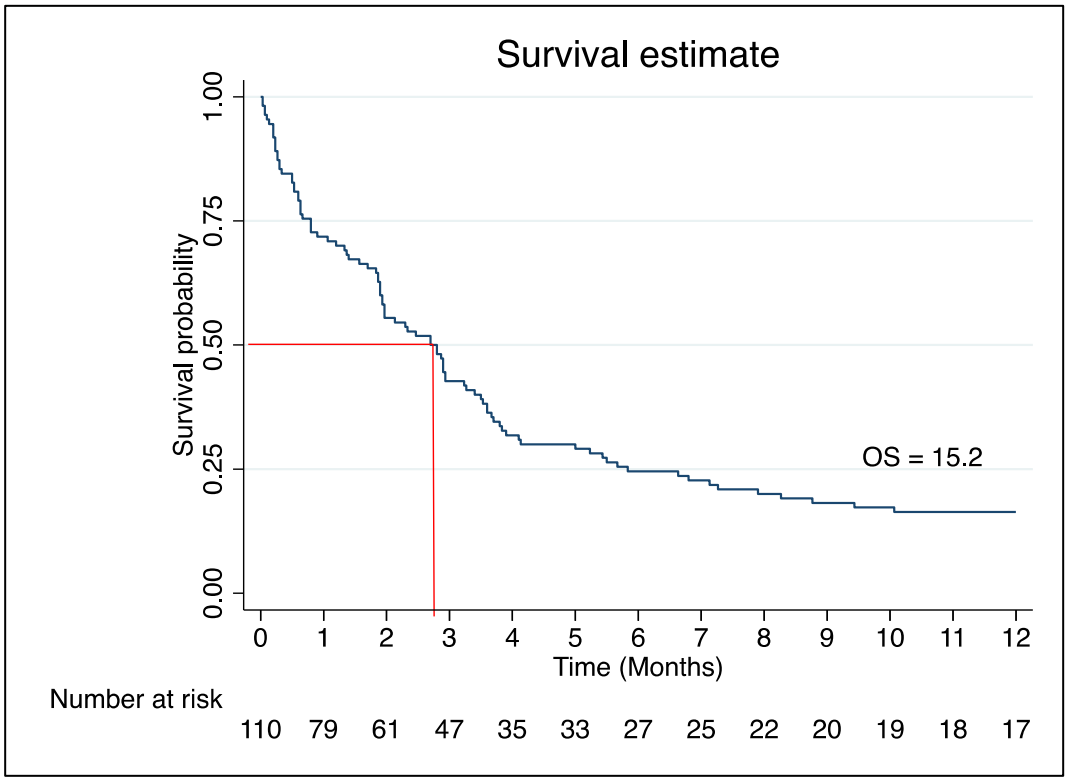
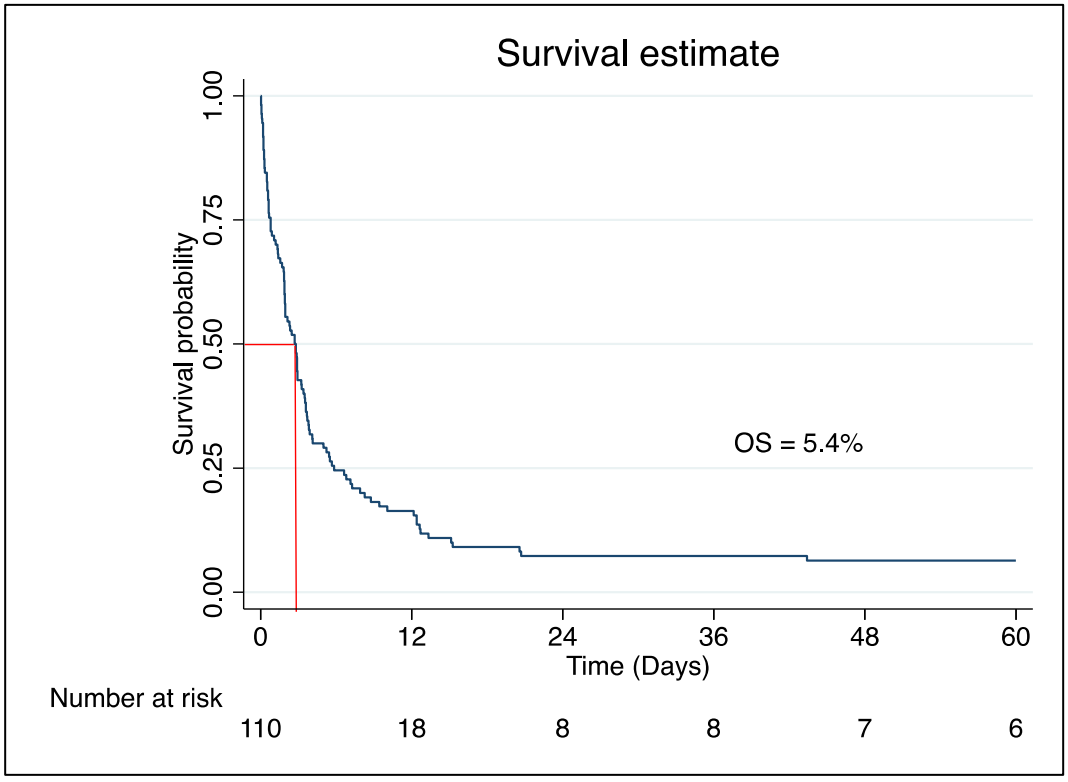


Table 4 Life table indicating the survival after each ninety days in a duration of one year

Interval in days	Total	Deaths	LTF	Survival	Std error	95% CI
0 - 90	112	65	0	0.420	0.0466	0.328 – 0.509
90 - 180	47	20	0	0.241	0.0404	0.167 – 0.323
180 - 270	27	9	0	0.179	0.0362	0.114 – 0.224
270-365	20	3	0	0.152	0.0339	0.093 – 0.224
Above 365	17	0	17	0.152	0.0339	0.093 – 0.224

4.6 Five year - Overall Survival for patients diagnosed with non-M3 AML

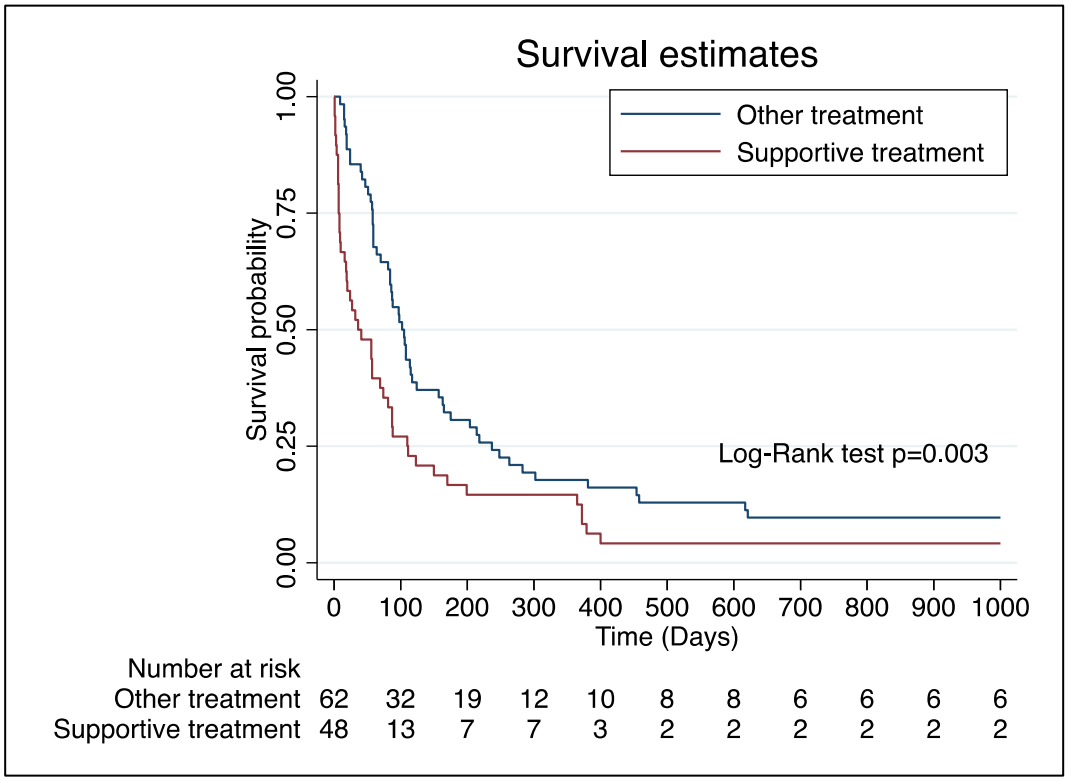
Figure 9: Kaplan Meier curve showing the five-year survival for patients diagnosed with non-M3 AML



4.7 Survival estimates for patients on treatment with chemotherapy +/- targeted therapy vs patients on supportive treatment alone.

The Kaplan-Meier curve shows the survival estimates for patients on chemotherapy +/- targeted therapy vs supportive treatment alone. Chemotherapy constituted those receiving either low-dose (LD) cytarabine or intensive chemotherapy. Targeted therapy refers to Venetoclax, which for some patients was given in combination with LD cytarabine. Supportive treatment refers to those patients who received supportive treatment alone and no chemotherapy. Patients who received chemotherapy +/- targeted therapy had a higher survival estimate compared to those who received supportive treatment alone. The difference was found to be statistically significant with a p-value of 0.003 (Figure 10).

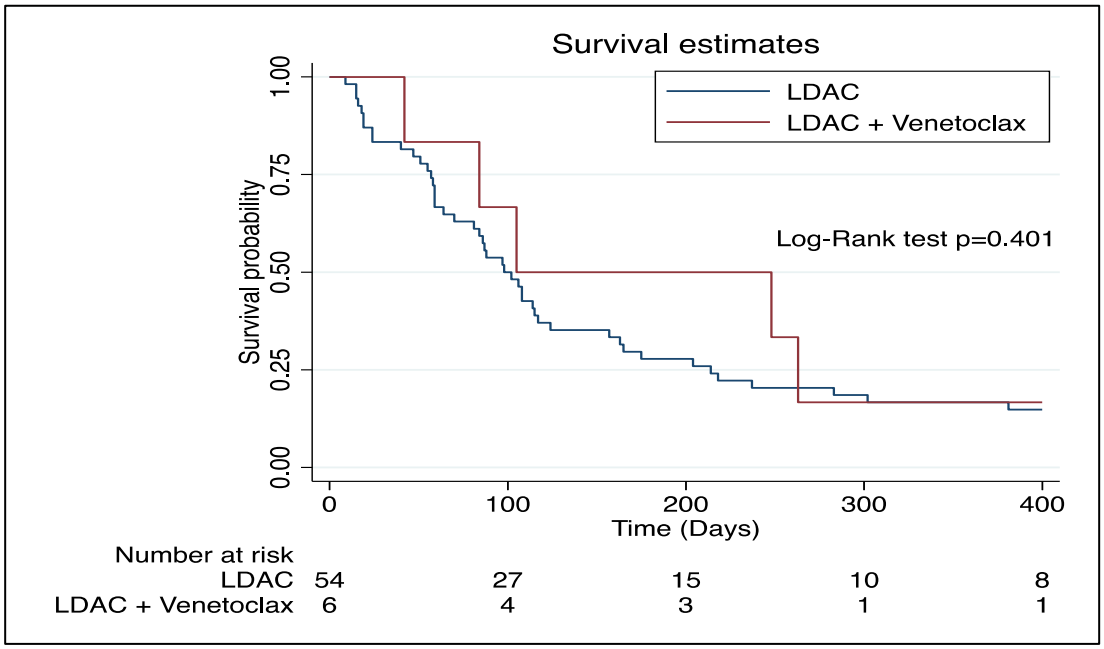
Figure 10: Log Rank Test for AML patients on supportive care alone versus AML patients on treatment with LD cytarabine/LD cytarabine + venetoclax or intensive chemotherapy in addition to supportive care



4.8 Survival estimates for patients on LD cytarabine vs. those on LD cytarabine with venetoclax.

No difference was observed in the survival outcomes between those patients on LD cytarabine (n = 54) and those on LD cytarabine with Venetoclax (n=6) (p=0.401) (Figure 11).

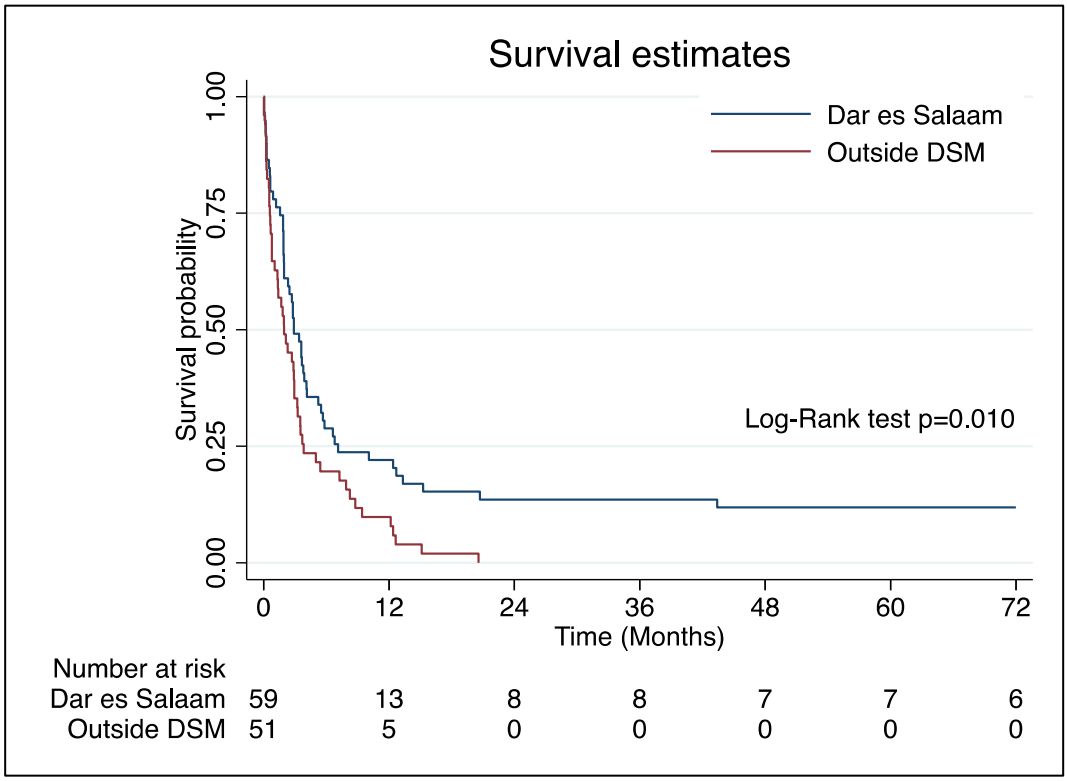
Figure 11: Log Rank Test for AML patients on low-dose cytarabine versus low-dose cytarabine + venetoclax



4.9 Survival estimates between the patients who resided in Dar es Salaam vs those who resided outside of Dar es Salaam

The figure below compares the survival estimates between the patients who resided in Dar es Salaam vs those who resided outside of Dar es Salaam. Patients who resided in Dar es Salaam (DSM) had a higher survival estimate compared to those who resided outside of DSM. The difference was found to be statistically significant with a p value of p = 0.010 (Figure 12).

Figure 12: Log Rank Test for AML patients residing in Dar es Salaam versus those residing outside of Dar es Salaam



4.10 Median survival time for acute myeloid leukemia

Table 5 illustrates the median survival time among AML patients based on the three treatment categories: supportive care alone, LD cytarabine and LD cytarabine with venetoclax. Among the patients receiving either LD cytarabine or LD cytarabine with venetoclax, the median survival time was 98 days and 105 days respectively. In contrast, patients receiving supportive alone treatment exhibit a notably lower median survival time of 36 days. Overall, regardless of the treatment regimen used, median survival time was 81 days.

Table 5 Median survival time for acute myeloid leukemia

Variable	Number of subjects	Survival time		
		25%	50%	75%
Supportive treatment alone	50	7	36	110
LD cytarabine	54	57	98	214
LD cytarabine with venetoclax	6	84	105	263
Total	110	24	81	175

4.11 Factors associated with the survival of patients with acute myeloid leukemia

In the univariate analysis, cox regression revealed that residing outside Dar es Salaam was associated with 67% increase in hazard for mortality in comparison with Dar es Salaam (cHR = 1.67, 95% CI: 1.12-2.49). For patients who received LD cytarabine as treatment it was associated with a 40% reduced hazard for mortality compared to those on supportive care alone (cHR = 0.60, 95% CI: 0.41-0.90). In the multivariate analysis residence outside Dar es Salaam demonstrated an increased hazard of mortality by 74% **(aHR**: 1.74, 95% CI: 1.15-2.64, p = 0.008). While for patients receiving LD cytarabine treatment the hazard for mortality was 39% lower compared to those who were on supportive treatment (aHR: 0.61, 95% CI: 0.40-0.93, p = 0.022). No association with survival was observed for the other variables (Table 6).

Table 6: Cox regression for factors associated with the survival of patients with AML

Variable	cHR(95% CI)	*p*-value	aHR(95% CI)	*p*-value
Sex				
Female	Ref		Ref	
Male	0.94(0.63-1.39)	0.755	0.95(0.64-1.42)	0.817
Age group				
Below 29	Ref		Ref	
30-49	1.41(0.81-2.45)	0.230	1.27(0.72-2.26)	0.408
Above 49	1.19(0.72-1.96)	0.491	1.38(0.81-2.35)	0.240
Place of residence				
Dar es Salaam	Ref		Ref	
Outside Dar es Salaam	1.67(1.12-2.49)	0.011	1.74(1.15-2.64)	0.008
Insurance status				
Insured	Ref		Ref	
Not insured	1.35(0.88-2.07)	0.176	1.23(0.73-2.07)	0.430
Comorbidities				
No	Ref		Ref	
Yes	0.87(0.53-1.44)	0.595	0.94(0.52-1.71)	0.851
De Novo AML				
No	Ref		Ref	
Yes	1.35(0.65-2.78)	0.422	1.01(0.47-2.14)	0.990
Treatment regimens				
Supportive treatment	Ref		Ref	
LD cytarabine	0.60(0.41-0.90)	0.013	0.61(0.40-0.93)	0.022
LD cytarabine and venetocla	0.43(0.17-1.08)	0.071	0.51(0.23-1.11)	0.090
Y_7_3	0.20(0.03-1.49)	0.118	0.28(0.03-2.99)	0.289

5.0 DISCUSSION

5.1 Prevalence and baseline characteristics of the patients of the patients diagnosed with AML

The prevalence of AML among the patients diagnosed with acute leukemia at MNH from 2018 to 2023 was 68%. This is similar to other studies done in East Africa; at a Cancer Institute in Uganda, a study done by Natukunda et al showed a prevalence of 58.4% among acute leukemias(37). A tertiary care hospital in Nepal saw 46.7% of patients with acute leukemia had AML (41).

Majority of the patients who were diagnosed and treated for AML resided in Dar es Salaam, Tanga, Pwani and Mbeya. Tanga and Pwani are within proximity of Dar es Salaam where the tertiary hospital is located, Mbeya is equipped with a specialized hospital having specialists inclusive of internal medicine and hematology who refer patients for a timely diagnosis and prompt management. The lower number of patients observed coming from other regions maybe a reflection of the limited diagnostic capacity in these regions or may be a result of referral to other tertiary facilities closer to these regions.

Majority of the patients were females, above 49 years old, uninsured, resided in Dar es Salaam and had de novo AML. The female predominance can be explained by the higher number of females present in the population; In 2022, Tanzania's female population amounted to approximately 33.13 million, while the male population amounted to approximately 32.37 million inhabitants(42). In other studies, the prevalence among males was found to be higher, 59.2% of the males were diagnosed with AML in a study done in Uganda and 71.7% in Nepal. Similarly, in Nepal, most of the patients were above 49 years old, however in Uganda majority of the patients were between 18 and 35 years old (37)(41).

5.2 Clinical features and laboratory characteristics

The majority of the patients had symptoms of anemia and fever. 16.1% of the patients had bone pain and bleeding tendencies. Few patients had organomegaly. These findings have been well-established in previous studies.

Utilizing the FAB classification system, M1 was the most prevalent type and M7 was the least prevalent type. Cases that could not be grouped into the FAB classification by looking at the morphology alone were referred to as Unspecified and they made up the largest proportion. All of the cases classified utilizing the FAB classification system were based on bone marrow morphology without flow cytometry. These results provide valuable insights into the subtype distribution within the AML cohort studied, highlighting the diversity of AML subtypes and emphasizing the urgent need for flow cytometry which would enable accurate classification for appropriate treatment strategies and prognostic assessments.

The variation in blood counts observed between different treatment time points and at diagnosis is an expected finding demonstrating response to these drugs. The hemoglobin and platelet counts were found to be highest after receiving chemotherapy.

5.3 Treatment and Survival Outcome

Only 1.7% of patients received standard of care. Standard care includes induction therapy and consolidation therapy. The cornerstones of intense chemotherapy continue to be cytarabine and anthracyclines.

After 365 days 17 patients were still alive resulting in a one-year overall survival of 15.2% with a median survival time of 81 days, this is slightly lower compared to the one-year survival outcome of Uganda which was 16.4% and the median survival time of 55 days. The five-year survival outcome in this study was 5.4 %. For patients with AML In the United States of America, the overall 5-year survival rate between 2010 – 2017 was 28%. The 5-year survival rate for patients between the ages of 15 and 39 years was 63%, whilst the rate for patients beyond 70 years was 5%, respectively.(33). In our study, most of our participants were younger, with a mean age of 47.2 years. However, the majority received palliative treatment, rather than standard of care. Treating AML patients with the standard of care regimen, including induction therapy

to achieve remission and consolidation therapy to prevent relapse, is crucial for improving outcomes and increasing the chances of long-term survival.

AML patients undergoing rigorous induction chemotherapy need specialized inpatient care because prolonged, severe neutropenia and thrombocytopenia carry a substantial risk of consequences. Critical care, supportive care, timely IV antibiotic administration for febrile neutropenia, platelet and red blood cell transfusions when necessary, nutritional support—including parenteral nutrition if necessary—specialized nursing, quick access to diagnostic tests, and other essentials are all necessary in a hospital setting. The intensive, prolonged inpatient care required for AML induction chemotherapy is best provided in a specialized cancer center with an experienced multidisciplinary team and robust supportive care capabilities.

For those patients who had received chemotherapy +/- Venetoclax, they had an improved chance of survival compared to those who were on supportive treatment alone. Attempt was made to compare the survival estimates for those patients on LD cytarabine vs. those on LD cytarabine with venetoclax; however, this was not possible due to the small sample of patients on LD cytarabine with venetoclax. Studies have shown with the addition of a BCL 2 inhibitor such as venetoclax to a hypomethylating agent improves survival outcomes in patient's ineligible for intensive chemotherapy.

In our cohort, factors that were associated with increased mortality included residing outside of Dar es Salaam and not being on chemotherapy. Reduced access to expert care, delays in diagnosis and treatment initiation, difficulties with treatment adherence, and difficulties with supportive care is probably the main cause of the negative impacts of distance. It can be difficult for patients who live distant from cancer treatment centers to travel significant distances for every clinic appointment and hospital stay. There was a correlation between living distant from the hospital and a worse chance of survival for AML patients. This discrepancy may be minimized by initiatives to increase access to specialist AML care, such as those supported by telemedicine and collaborations with regional doctors. Patients who live far away should be recognized early and given more assistance.

One strength of this study is that it is the first study in Tanzania to report on survival outcomes of patients with AML.

The small number of patients on LD cytarabine with venetoclax and those who had undergone intense chemotherapy placed limitations on the study. Additionally, some of the patients could not be subclassified since the diagnosis was determined solely based on bone marrow morphology without the use of immunophenotyping. Since there was no record on the patients' performance status, no study was done to see how it related to survival results. Future research should use standardized assessments of performance status, such as the Karnofsky performance status or the Eastern Cooperative Oncology Group (ECOG) scale. Correlating performance status with survival outcomes can be greatly aided by this data.

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The prevalence of AML was 68% among acute leukemias at MNH. Majority of the patients were females, above 49 years old, uninsured and had de novo AML. Most of the patients presented with fever and symptoms of anemia. The one-year overall survival was 15.2% with median survival time of 81 days. There was increased hazard of mortality for patients who resided outside of DSM and those on supportive treatment alone. We were unable to evaluate the survival rates of patients on LD cytarabine with venetoclax to those on LD cytarabine alone because of the small number of patients on this combination.

6.2 Recommendations

- Future prospective studies should be conducted on patients with AML receiving LD cytarabine and venetoclax at the Muhimbili National Hospital in order to be able to determine the survival outcome.

- Strong emphasis should be placed on the need for risk stratifying patients with AML diagnosed at MNH, inclusive of counselling patients for the need of molecular studies. Currently at MNH molecular studies are not being offered, however some of the molecular studies are being offered at the Muhimbili University of Health and Allied Science, a collaboration between the both institutions would be beneficial.

- Need for recording performance status (ECOG) in patients' files and for immunophenotyping to be done. Recently this service is now being offered and samples do not need to be sent to exterior facilities which would facilitate a shorter turn around time

- Currently an area equipped and suitable for standard of care exists at the MNH Mloganzilla Campus where recently the MNH has successfully completed its third autologous stem cell transplant camp. This can be seen as a stepping stone and paving way for the new era where allogeneic stem cell transplant can be done for patients with AML.

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APPENDIX

APPENDIX 1: DATA COLLECTION TOOL

File number:

Age:

Sex:

Residence:

Date of admission:

Date of discharge:

Co morbidity:

BMI:

ECOG:

Type of AML

De novo AML:

Secondary AML:

Unspecified:

Presenting Signs:

Please state-

Presenting Symptoms:

Mode of diagnosis

Morphology

Flow cytometry

Date of BMA and trephine biopsy:

Percentage of blasts:

FAB classification:

Results of flow cytometry:

Results of CBC:

Number of transfusions

PRBCs: ……

Platelets: …….

Please circle the treatment regimen:

None

7+3

LD cytarabine

For the treatment regimen selected state:

Date treatment was initiated: ……

Date of completion: …….

Reason for treatment holiday/Withdrawal: ……

Number of completed cycles: ……

Side effects from treatment: …….

Survival outcome (Please circle)

Alive Dead Unknown status

If dead, state:

Date of death…….

Cause of death: …….

Appendix 2: Data Collection Tool (Swahili Version)

Namba ya faili:

Umri:

Jinsia:

Makazi:

Kabila:

Hospitali ukotokea:

Tarehe ya kulazwa:

Tarehe ya kutoka hospitali:

Magonjwa ambatanishi:

BMI:

ECOG:

Aina ya AML

De novo AML:

Secondary AML:

Unspecified:

Dalili za mwanzo za Ugonjwa:

Tafadhali taja-

Viashiria na dalili nyingine za ugonjwa:

Vipimo vilivyo gundua ugonjwa

Morphology

Flow cytometry

Tarehe ya kipimo cha Uboho:

Percentage of blasts:

FAB classification:

Majibu ya flow cytometry:

Majibu ya CBC(wingi wa damu):

Idadi ya damu uliyo ongezwa

PRBCs……

Platelets: …….

Tafadhali zungushia aina ya matibabu aliyo pata:

hakuna matibabu

7+3

LD cytarabine

Kwa tiba uliyochagua taja:

Tarehe ya kuanza tiba: ……

Tarehe ya kumaliza tiba: …….

Sababu ya Kuacha tiba: ……

Idadi ya mizunguko ya tiba uliyomaliza: ……

Madhara ya tiba: ……..

Hali ya sasa ya mgonjwa(tafadhali zungushia jibu)

Yupo hai Amefariki Haijulikani

Kama amefariki taja:

Tarehe ya kifo:…….

Sababu ya Kifo: ……

Appendix 3a: Approval for ethical clearance

UNITED REPUBLIC OF TANZANIA

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATION

Ref. No.DA.282/298/01.C/1998 Date: 19/12/2023

MUHAS-REC-12-2023-1998
MICHELLE MUNROE
COLLEGE OF MEDICINE
MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: ACUTE MYELOID LEUKEMIA IN TANZANIA: CLINICAL FEATURES, LABORATORY CHARACTERISTICS AND SURVIVAL OUTCOME

Reference is made to the above heading,

I am pleased to inform you that the Chairman has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 19/12/2023
EXPIRATION DATE OF APPROVAL: 19/12/2024

STUDY DESCRIPTION:
Purpose:

The purpose of this retrospective cohort study is to determine the clinical features, laboratory characteristics and survival outcomes of patients with Acute myeloid leukemia treated with different regimens in Tanzania.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided:
https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%2014801.pdf and in the MUHAS archives.

Appendix 3b: Approval for ethical clearance

The PI is required to:

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain Data Transfer Agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain Material Transfer Agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country.
8. Apply for and obtain permission to publish the results from National Institute for Medical Research. The application should be before submitting to a publisher and not concurrently through the email publications@nimr.or.tz.
9. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
10. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
11. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.

Muhimbili University of Health and Allied Sciences
DIRECTOR
Research, Publications & Innovations
Box 65001

Dr. Nahya Salim Masoud,
Chairperson, MUHAS Research and Ethics Committee

Appendix 4 : Introduction letter to MNH

UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote;
Ref. No. HD/MUH/G.54/2021

10th January 2024

The Executive Director,
Muhimbili National Hospital,
P.O. Box 65000,
DAR ES SALAAM

Re: INTRODUCTION LETTER

We would like to inform you that the bearer of this letter is Michelle Munroe with Reg. No. HD/MUH/G.54/2021 is a student at Muhimbili University of Health and Allied Sciences (MUHAS) "pursuing MMed. Haematology/Blood Transfusion.

As part of her studies, she will be doing an elective research titled: "**Acute Myeloid Leukemia in Tanzania: Clinical Features, Laboratory Characteristics and Suirvival Outcome"** she is being supervised by Dr. Clara Chamba from MUHAS and Dr. Yonazi Mbonea from MNH.

The research has been approved by the Chairman of University Senate.

Kindly provide her the necessary assistance to facilitate the conduct of her research.

We thank you for your cooperation.

Ms. Victoria Mwaniwa
For: DIRECTOR, POSTGRADUATE STUDIES

c.c Michelle Munroe

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam: Tel. G/Line: +255-22-2150302/6; Ext. 1015; Direct Line:+255-22-2151378;Telefax:+255-22-2150465;E-mail:dpgs@muhas.ac.tz;Web:https://www.muhas.ac.tz

8.6 Appendix 5: Letter of permission to collect data at MNH

THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

MUHIMBILI NATIONAL HOSPITAL

In reply please quote:

Ref. No.: MNH/CRTCU/Perm/2024/020 Date: 11th January, 2024

Head of Department
Medical Records
Muhimbili National Hospital

RE: PERMISSION TO COLLECT DATA AT MNH

Name of Student	**Michelle Munroe**
Title	**"Acute Myeloid Leukemia in Tanzania: Clinical Features, Laboratory Characteristics and Survival Outcome at MNH."**
Institution	Muhimbili University of Health and Allied Sciences
Supervisors	Dr. Clara Chamba (MUHAS) Dr. Yonazi Mbonea (MNH)
Period	11th January 2024 to 30th April, 2024

Approval has been granted to the above principal investigators to collect data at MNH. Dissemination of study findings at MNH shall be overseen by **Dr. Yonazi Mbonea (**MNH) supervisor.

Kindly ensure the named principal investigator abide to the ethical principles and other conditions of the research approval.

Sincerely,

Pallangyo

Dr. Charles K. Pallangyo
For: Head of Clinical Research, Training and Consultancy Unit

HEAD, TEACHING, RESEARCH & CONSULTANCY UNIT
P.O. Box 65000
DAR-ES-SALAAM
MUHIMBILI NATIONAL HOSPITAL

c.c DICT
c.c Dr. Yonazi Mbonea
c.c Michelle Munroe

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