CHRONIC MYELOID LEUKEMIA IN TANZANIA: CLINICAL PROFILE AND FIVE-YEAR SURVIVAL

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CHRONIC MYELOID LEUKEMIA IN TANZANIA: CLINICAL PROFILE AND FIVE-YEAR SURVIVAL

By

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A Dissertation Proposal submitted in partial fulfillment of the requirement for the degree of Master of medicine in Clinical Oncology –

Muhimbili University of Heath and Allied Sciences

October, 2024

CERTIFICATION

The undersigned certifies that he has read and hereby recommends for acceptance by the The Muhimbili University of Health and Allied Sciences a dissertation entitled "*Chronic myeloid leukemia in Tanzania: clinical profile and five-year survival"* in partial fulfillment of the requirements for the degree of Masters of Medicine in Clinical Oncology Muhimbili University of Health and Allied Sciences.

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DECLARATION AND COPYRIGHT

I, **Kelvin Mbelekwa** hereby declare that this **dissertation** is my 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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DEDICATION

This dissertation is dedicated to all the courageous individuals who have faced the challenges of cancer, both past and present. Your unwavering strength, resilience, and determination in the face of adversity have been a constant source of inspiration.

ABSTRACT

Keywords: Chronic Myeloid Leukemia (CML), Tanzania, Five-year Survival, Tyrosine Kinase Inhibitors (TKIs), Ocean Road Cancer Institute (ORCI)

Background: Many patients with CML in Tanzania present with a bulky disease at diagnosis. However, limited information is available on the specific burden of CML in Tanzania. Despite over 20 years of CML treatment in Tanzania, little is known about the sociodemographic profiles, clinical characteristics, and survival of patients with CML in Tanzania. Currently, only ORCI and KCMC are the two institutions in Tanzania that receive free Tyrosine Kinase Inhibitor medications thanks to a donation from the Max Foundation. With this exclusive availability of medications in these two hospitals, more CML cases are likely to be attended in these hospitals compared to the past years. This study aims to investigate the disease burden and epidemiologic trends of chronic myeloid leukemia (CML) in Tanzania to bridge the knowledge gap between what is already known and the unknown about the disease in our locality.

Objective: To determine the trend of CML incidence and the five-year overall survival of the patients who attended ORCI between January 2015 to December 2023.

Materials and methods: This was a retrospective analysis of patients diagnosed and treated for chronic myeloid leukemia at Ocean Road Cancer Institute (ORCI) for the past 9 years. All patients with a histologically confirmed diagnosis of chronic myeloid leukemia from 2015 to 2023 were included. Data was gathered from the digital hospital record system and files of patients. Data was analyzed using STATA version 17. Descriptive statistics such as percentage and mean were used to describe the demographic, clinical, and laboratory characteristics of the patients. The chi-square test was used to test the trend in a number of new CML cases at ORCI between 2015 to 2023. Kaplan Meier estimation was used to determine the survival. A p-value of 0.05 was used to assess the significance of the obtained results.

Results: The study analyzed 340 CML patients at ORCI's clinic in Tanzania. The number of new patients increased linearly between 2015 and 2023, with a dip during the COVID-19 pandemic. Younger patients predominate with a mean age of 38.5 years at diagnosis, highlighting the socioeconomic impact. The study found a high 5-year survival rate of

90.6%, comparable to high-income countries. Factors associated with CML survival included age at diagnosis, absolute monocyte count, and percentage of blasts at diagnosis. The study highlights the need for sustainable CML treatment and better patient tracking in low -resource setting.

Conclusion: Chronic Myeloid Leukemia is among the most frequently diagnosed leukemia in Tanzania. The data reveals an upward trend in CML cases at ORCI from 2015 to 2023, likely due to improved diagnostics and decentralized services. Younger patients predominate, highlighting the socioeconomic impact. Survival rates are promising; however, challenges persist in the sustainability of the treatment program

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LIST OF ABBREVIATIONS

ABL-BCR	Gene-Abelson-Breakpoint Cluster Region Gene
CML	Chronic myeloid leukemia
FISH	test- fluorescence in situ hybridization
GIPAP	The Glivec International Patient Assistance Program
KCMC	Kilimanjaro Christian Medical Centre
LMICs	Low- and middle-income countries
ORCI	Ocean Road Cancer Institute
Ph	Chromosome-Philadelphia Chromosome
SPSS	Statistical Package for the Social Sciences
TKI	Tyrosine Kinase Inhibitors
WHO	World Health Organization
GLOBCAN	Global Cancer Observatory
Ahr	Adjusted Hazard Ratio

DEFINITION OF KEY TERMS

Disability-adjusted life years (DALY)-the total number of years lost to early death and years spent disabled as a result of a sickness or health condition that is common among a population**.**

The sociodemographic index (SDI) as addressed in the global study is a figure based on total fertility rate, educational attainment, and average annual income per person indicating the place on the development spectrum that various nations or other geographic locations occupy. For this particular study, SDI is based on, insurance status and employment status.

Keywords:

Chronic Myeloid Leukemia (CML), Tanzania, Epidemiologic Trends, Sociodemographic Profile, Clinical Characteristics, Tyrosine Kinase Inhibitors (TKIs), Ocean Road Cancer Institute (ORCI)

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Chronic myeloid leukemia (CML) is a slowly progressing cancer of the bone marrow and blood, primarily affecting white blood cells. It is characterized by the overproduction of granulocytes and is caused by a chromosomal translocation t(9;22), resulting in the BCR-ABL fusion gene, which drives uncontrolled cell growth. In Sub-Saharan Africa, the prevalence of non-communicable diseases, including CML, is increasing, with Tanzania reporting 40,464 new cancer cases in 2020, 10% of which were hematological malignancies. Studies indicate that CML is prevalent in other African countries such as Sudan, Ethiopia, and Libya, with younger patients being diagnosed compared to those in high-income countries. In South Africa, CML also shows a notable incidence among younger populations, with studies indicating a median age of diagnosis around 34 years (1,2).The incidence of CML varies by age and gender, with a male-to-female ratio of 1.2-1.7 and a higher frequency in older populations. Treatment for CML has evolved significantly with the introduction of tyrosine kinase inhibitors (TKIs), such as imatinib, dasatinib, and nilotinib, which have improved five-year survival rates from approximately 20% to over 90%. However, access to these medications remains a challenge in many LMICs due to economic constraints and healthcare infrastructure limitations. For example, in rural Rwanda, patients have been treated successfully with the support of international programs like GIPAP (Glivec International Patient Assistance Program), although such programs are limited and often concentrated in urban centers(3).In Tanzania, imatinib is the primary treatment option, although second-generation TKIs are also available.

CML presents in three phases: chronic, accelerated, and blast phase. The most common clinical indicator is an abnormal white blood cell count. Research on CML in Africa is limited; thus, understanding patient demographics and survival rates is crucial for improving treatment strategies. This study aimed to evaluate current management practices for CML in Tanzania while identifying time trends in the number of new cases and patient characteristics to inform targeted prevention and treatment efforts. Insights gained may enhance patient care and guide policy decisions regarding CML management in the region.

1.2 Statement of Problem

According to a systematic analysis conducted for the Global Burden of Disease Study 2017, the incidence rate of CML was around one case per 100,000 people worldwide in 2018, and it represents 15% of instances of newly diagnosed leukemias(4). The 2019 Global Burden of Disease (GBD) survey found that there were approximately 1639 new cases annually of CML in the Eastern Sub-Saharan African region, which includes Tanzania(5)**.** However, the incidence and prevalence of CML in Tanzania and how it has changed over time is unknown. With improving diagnostic methods and technology, CML has been more frequently diagnosed in Tanzania. To better understand the disease burden over time, it is important to explore the patterns of patients with CML, social demographic characteristics and survival. Understanding the disease time trend in the number of new cases, will likely lead to improved patient care by assisting in the evaluation of the effectiveness of the current practice and supporting the policymakers in their decision-making.

1.3 Conceptual framework

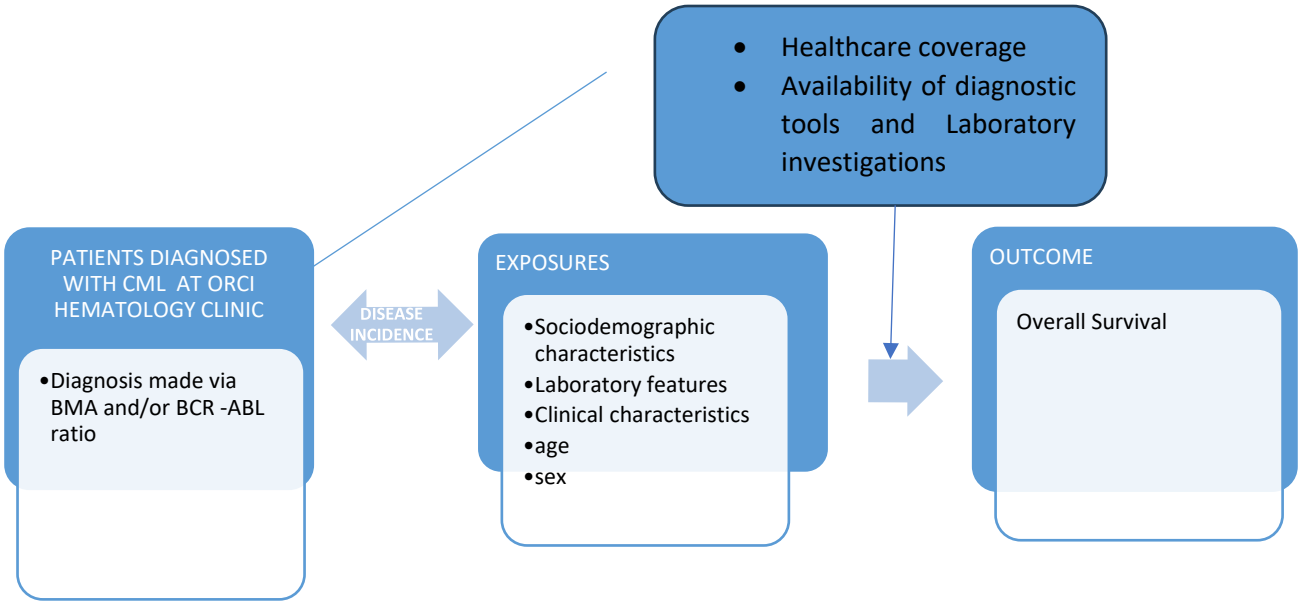


Figure 1: The conceptual framework showing factors affecting CML diagnosis, treatment, disease burden and survival.

Among the reasons which could contribute to early CML diagnosis are social demographic factors such as the financial-economic status of the patient, health-seeking behaviour, level of education and geographical factors like the distance to the major referral hospitals. These factors(exposures) will consequently influence the trends of CML burden and survival(outcomes) in Tanzania**.** Higher survival rates and better treatment results can result from early CML identification (6). The patient's prognosis can be determined by factors influencing treatment access, such as financial hardship and insurance coverage, as well as by the accessibility of diagnostic equipment and laboratory tests. Understanding Tanzania's CML disease burden will require consideration of variables like the incidence and prevalence of CML in the nation as well as the accessibility and availability of treatment. The clinical manifestations of CML can vary depending on the phase of the disease at presentation. Symptoms can vary with patients presenting with fatigue, weight loss, bleeding

and splenomegaly with more severe symptoms seen in the blast phase(7). Tyrosine kinase inhibitors (TKIs) used in chronic-phase CML patients have a median survival that is anticipated to resemble normal life expectancy.

1.4 Rationale

Studies done in Sudan and Ethiopia report CML to be the most commonly diagnosed leukemia in adults(8,9). However, there is a dearth of information on CML in Tanzania despite studies on the occurrence and outcomes of CML in other nations. To comprehend the severity of the disease, it is crucial to ascertain the time trends in a number of new patients diagnosed annually, which will guide focused initiatives to enhance CML diagnosis, care, and management in Tanzania. Knowing the social demographics of CML patients in Tanzania, including their age, gender, location, and health insurance status, might assist in identifying potential risk factors for the illness and guide targeted preventative and treatment measures. By describing the clinical and laboratory characteristics of CML patients in Tanzania, such as the disease stage at diagnosis, it is possible to spot deficiencies in the healthcare system and provide guidelines for effective treatment. Understanding the survival of CML patients in Tanzania can assist in pinpointing the elements that influence favourable or unfavourable results and guide the creation of effective treatment and supportive care plans. The findings from this research can be utilized by the policymakers to assess the CML management strategies currently in place, which primarily rely on prescription drugs from outside donors, to plan for a more reliable supply of medications in the future.

1.5 Research Questions

i. What is the time trend in the number of new Chronic myeloid leukaemia patients at ORCI from 2015 to 2023?

ii. What are the clinical characteristics of patients with Chronic myeloid leukaemia at ORCI?

iii. Which treatment options are used for patients with Chronic myeloid leukaemia at ORCI?

iv. What is the 5year survival among patients treated for Chronic myeloid leukaemia at ORCI?

1.6 Objectives

1.6.1 Broad Objective

To describe the clinical profile, **time trend** and five-year survival of patients diagnosed with CML in Tanzania between 2015 to 2023.

1.6.2 Specific Objectives

i. To identify the patterns and changes in the number of new CML cases between 2015 to 2023

ii. To explain the sociodemographic profile of patients with Chronic myeloid leukemia at ORCI between 2015 to 2023.

iii. To define the clinical features of patients with Chronic myeloid leukemia at ORCI.

iv. To determine the five-year overall survival and factors associated with survival among patients treated for Chronic myeloid leukemia who attended ORCI between 2015 to 2023.

1.7 Literature review

Epidemiology

The CML incidence distribution varies with age, gender, and region, according to the data that is currently available(10)(11). In different nations, the annual incidence of CML ranges from 0.4/100,000 to 1.75/100,000 people(12–14). CML is uncommon in children under the age of 14 (0.7/million children/year), and its frequency rises with age(15). Additionally, the male/female ratio of 1.2-1.7 indicates that CML affects men more frequently than it does women(12,16,17). From 1990 to 2017, the global burden of CML disease gradually decreased. Higher Social Development Index countries had a notable reduction in the burden of CML. In contrast, the incidence cases, mortality cases, and Disability-adjusted life years (DALY) of CML in lower SDI exhibited an increased trend due to population growth (18). With a median age of 57–60 years at diagnosis, the crude annual incidence of CML in Europe is between 0.7 and 1.0/100,000. The WHO claims there is no evidence of a link with race or ethnicity, and the data from the United States of America show an incidence rate of 1.6/100,000(19). According to the American Cancer Society's most recent statistics, there will be roughly 8,930 new cases of CML diagnosed (5,190 in males and 3,740 in women).In the United States, approximately 1,310 people will die from CML (780 men and 530 women), and 1 in 526 persons will develop CML during their lifetime (20). According to a 30-year study done in the greater Mumbai area of India, the incidence of CML rose from 0.5 per 100,000 people in 1976 to 1.5 per 100,000 people in 2006(21). According to a different study, India was reported to have the highest number of CML-related deaths and disability-adjusted life years (DALYs) worldwide(4). The time trends in the occurrence of CML has demonstrated noteworthy patterns in its incidence throughout various global regions between 1990 and 2017.From roughly 31,752 in 1990 to 34,179 in 2017, there were 34,179 annual incident cases of CML, a minor rise of approximately 7.64% over this time, indicating a stable incidence in number of cases.Consistently declining globally, the ASIR(age-standardized incidence rate) was most noticeable in nations with high sociodemographic indexes (SDI)(18). Ethiopia stands out as having the highest age-standardized death rate from CML in 2019, with 1.89 deaths per 100,000 people, suggesting that the country has a high disease burden. The general trend implies that whereas high-SDI locations have

witnessed reductions in CML incidence and death, lower-SDI areas are facing increasing rates due to variables such as population expansion and poor access to healthcare services(4).

The treatment and natural history of CML have changed significantly in recent years with the introduction of tyrosine kinase inhibitors. The 5-year survival rate has improved from little more than 20% to over 90%(22). The estimated 8-year survival rate in the United States of America rose from less than 20% prior to 1990 to 45% between 1991 and 2000 and 75% since 2001(23). In 93 countries, the Glivec (24)International Patient Assistance Programme (GIPAP) has established a direct-to-patient drug donation model under the supervision of the patients' oncologists. Despite the difficulties in providing cancer care in low- and middle-income countries, the program's effect on survival revealed a 5-year survival rate of 89%, which is excellent and, when adjusted for patients' prognosis at the time of diagnosis, compares favourably to survival in high-income countries(25). A number of factors, including treatment effectiveness, patient age, healthcare quality, hereditary factors, and disease stage upon diagnosis, affect the overall five-year survival rate for CML. The prognosis for many CML patients has changed as a result of advancements in targeted medicines, which have greatly increased survival rates in comparison to historical data(26).The most prevalent hematologic cancer in Africa is CML, and patients typically present with a bulky disease with a late onset. There are difficulties in getting treatment, and there are few data on hematologic cancers in Tanzania(19,27,28).

Clinical Presentation

On the clinical manifestation of Chronic Myeloid Leukemia (CML) in Africans, there is scant information available. Nevertheless, some research has been done in Central, Southern, and East Africa. A study done in Central Africa found that the clinical and hematological manifestations of CML are changing, most likely as a result of the development of modern clinical practice along with an increase in physician density, higher awareness of the disease among clinicians, and other factors (29). According to findings from a different study carried out in Southern Nigeria, the clinical symptoms were used to make the diagnosis of CML(30). In 1976, modest research involving 25 patients and examining the demographic and clinical characteristics of CML in black South Africans was published(1). The clinical manifestation of CML in Africans, however, was not specifically covered in this study. Therefore, there is not enough evidence to support the idea that Africans and other populations' clinical

presentations of CML differ significantly from one another. An abnormal white blood cell count is the most typical indicator of CML and is frequently discovered through blood tests for unrelated medical conditions or during routine checkups. CML can present in three different phases: chronic phase, accelerated phase, and blast phase. The symptoms of anemia such as fatigue and malaise, accompanied by splenomegaly are the ones that CML exhibits most frequently when it is in the chronic phase. A mass effect from splenomegaly may result in pain, early satiety, or left upper quadrant fullness. Additionally, CML can result in basophilia, which releases histamine, thrombocytopenia or platelet dysfunction leading to bleeding or thrombocytosis causing thrombosis. Headaches, bone pain, fever, joint pain, bleeding, infections, and lymphadenopathy are among the symptoms that are more prevalent as CML enters the accelerated phase or blast phase. (31)

The quantity of immature white blood cells in the blood or bone marrow indicates which stage of CML is present. In the chronic phase, which affects the majority of CML patients, there are less than 10% blasts in the blood or bone marrow. The minor symptoms are amenable to conventional therapies. Blasts are more abundant and occasionally there are new chromosomal alterations during the accelerated phase. More than 20% of the cells in the blood or bone marrow are blasts during the blast phase, and the illness acts more like acute leukemia. Without proper therapy, the chronic phase of CML will eventually transition into the accelerated phase, which will then transition into the blast phase in roughly 3 to 4 years following diagnosis(6,32).

Diagnosis

The results of the blood cell count and a review of the blood film can be used to make a preliminary diagnosis of CML. Most individuals have lower blood hemoglobin levels when they are diagnosed. At the time of diagnosis, the total leukocyte count is almost invariably higher than $25x10^9$/L, and at least half of the patients have a total white count above $100x10^9$/L. Hematopoietic tissue makes up between 75 and 90 percent of the bone marrow test's volume, with fat levels noticeably lower. The test would also show a noticeable hypercellularity. In contrast to the typical granulocytic-to-erythroid ratio of 2:1 to 4:1, granulopoiesis is dominating, with values between 10:1 and 30:1. More than 90% of patients with clinical and laboratory symptoms that meet the criteria for the diagnosis of CML also have the t(9;22)(q34;q11)(BCR-ABL1) by FISH and nearly all patients have the Ph

chromosome (22q), as determined by G-banding, in their marrow and nucleated blood cells. The Ph chromosome is found in all blood cell lineages, including erythroblasts, granulocytes, monocytes, megakaryocytes, T- and B-cell progenitors, although it is absent from the majority of blood B lymphocytes and the majority of T lymphocytes. (33,34).

Treatment

The introduction of BCR-ABL1 tyrosine kinase inhibitors (TKIs) has significantly altered the therapeutic result for CML patients over the past 20 years(35). The FDA approved imatinib mesylate (imatinib) in 2002 as the first TKI for use in the treatment of CML. Nilotinib, dasatinib and bosutinib second-generation TKIs, were later authorized for use in the first-line setting. This approval was based on higher rates of cytogenetic and molecular response with standard time periods and lower rates of conversion to accelerated or blast phase in comparison to imatinib(33). The third-generation TKIs are ponatinib and asciminib, which are approved for patients with refractory CML(24,36). The study done in Northern Tanzania has shown that there are still barriers to treatment access and even if CML treatment is available in low- and middle-income countries (LMICs) is mostly by donation or government assistance(19). A different study done in remote Rwanda demonstrated that GIPAP-facilitated CML treatment is efficient and secure in LMICs. The studies generally indicate that CML treatment is accessible in several African nations, however, there are still barriers to receiving treatment(3).

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 Study design

This was a retrospective observational study. It was a non-randomized, non-interventional analysis of current patients, care-related, and outcome-related data (files and electronic data).

2.2 Study area

The study took place at the Ocean Road Cancer Institute (ORCI), a government-owned specialized cancer treatment center in Tanzania. Located in Dar es Salaam city, along the Indian Ocean, it is a comprehensive, specialized center for cancer care which also functions as a teaching hospital Numerous patient services are provided by ORCI, such as laboratory investigations, diagnostic imaging, chemotherapy, radiotherapy, palliative care, cancer screening, and a special hematology clinic with mainly CML patients**.** Hard drives and other storage systems are used by ORCI's Information Technology department (IT) to store patients' electronic data. The electronic data network created for the organization known as INAYA provides access to this information. Certain vital patient data is also available in hard copy files that are kept in the departments of Records and Cancer Registry repositories. Every month, the ORCI hematology clinic sees roughly 200 patients. Approximately four new cases of the disease are seen each month at the twice-weekly clinic, which is mostly attended by patients referred from all over the country. The majority of the CML patients attend the follow-up clinic and have been clients for several years. These patients receive weekly attention from a single permanent hematologist. Tyrosine kinase inhibitor drugs that are been used by CML patients at this hospital have been made available through a partnership between the "Max Foundation, (a nongovernmental organization dedicated to accelerating health equity by improving access to cancer treatment and care for patients in low- and middle-income countries), together with ORCI, and are prescribed by the clinic in three-month intervals for a ninety-day supply of pills. The patient is scheduled to return for regular blood tests, such as the BCR-ABL ratio test, which is ordered on an annual minimum basis, as well as medication refills.

2.3 Study population

Patients diagnosed with CML, who attend the hematology clinic at Ocean Road Cancer Institute.

2.4 Selection of Participants

Patients were selected from the records management system from ORCI. All patients with a confirmed diagnosis of chronic myeloid leukemia by bone marrow biopsy and confirmed presence of Philadelphia chromosome from January 2015 to December 2023 were included in the study

2.5 Eligibility criteria

2.5.1 Inclusion criteria

All patients diagnosed with CML from January 2015 to December 2023 treated at ORCI were included in this study.

2.5.2 Exclusion criteria

Patients diagnosed with CML between January 2015 to December 2023 with missing data on confirmatory CML diagnosis.

2.6 Sample size estimation

The estimation of sample size was based on a study conducted by Umeh et al, which reported an estimated 5 years overall survival of 89% for the CML patients enrolled in GIPAP (25). Using an online tool from https://clincalc.com/stats/samplesize.aspx(an online sample size calculator for medical professionals) an estimated sample size was obtained. The aim was to include all CML patients who met the inclusion and exclusion criteria between 2015 to 2023.

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

$$q_0 = 1 - p_0$$

$$q_1 = 1 - p_1$$

$$N = \frac{0.89 * 0.11 \left\{ 1.96 + 0.84 \sqrt{\frac{0.84 * 0.16}{0.89 * 0.11}} \right\}^2}{(0.84 - 0.89)^2}$$

$$N = 340$$

Alpha=0.05

Beta=0.2

Power=0.8

Z = level of confidence (1.96 for 95% confidence level)

P0 = proportion of the population was 89%

P1=proportion of the study group is 84%

N=340, with a study power of 80%

The estimated sample will be 340 patients with CML.

2.7 Data Collection

We gathered data from ORCI computers and patients' physical files from the Records department. The information was entered into a computer spreadsheet. Data on variables such as age, gender, region, occupation, and insurance status were gathered. Additionally, presence of clinical features such as symptoms of anaemia, fever, bleeding tendencies, lymphadenopathy, and organomegaly, were recorded. Laboratory parameters such as total leucocyte count, differential leukocyte counts, haemoglobin level, platelet count, BCR-ABL ratio or Fluorescence In Situ Hybridization(FISH test) , and treatment for the patient was also among the data which were collected

2.8 Data analysis

STATA version 17 was used to analyze the collected data. To describe the demographic, clinical, and laboratory characteristics of the patients, descriptive statistics like percentage, mean and median were used. Categorical variables such as gender, year of diagnosis, place of residence, occupation, and insurance status together with continuous variables such as age and complete blood count at diagnosis were summarized in an Excel sheet and analyzed. The survival outcome was calculated using the Kaplan-Meier method. Cox regression was used to determine factors associated with survival outcomes in the patients. The chi-square test for trend was utilized to ascertain whether the proportions of new CML diagnoses showed a linear trend from 2015 to 2023. To evaluate the significance of the results, a p-value of 0.05 was used.

2.9 Ethical consideration

The Ethical Clearance Board (IRB) of Muhimbili University of Health and Allied Sciences granted approval to conduct the study. Patients' identities were kept anonymous to protect their privacy.

2.10 Publication and dissemination

The findings of this study were summarized in a dissertation and made public. The main manuscript with the title 'Trend and survival of Chronic Myeloid Leukemia in Tanzania' will be submitted to a reputable peer reviewed journal for publication. The principal investigator will publish this study within a year of its completion.

CHAPTER THREE

3.0 RESULTS

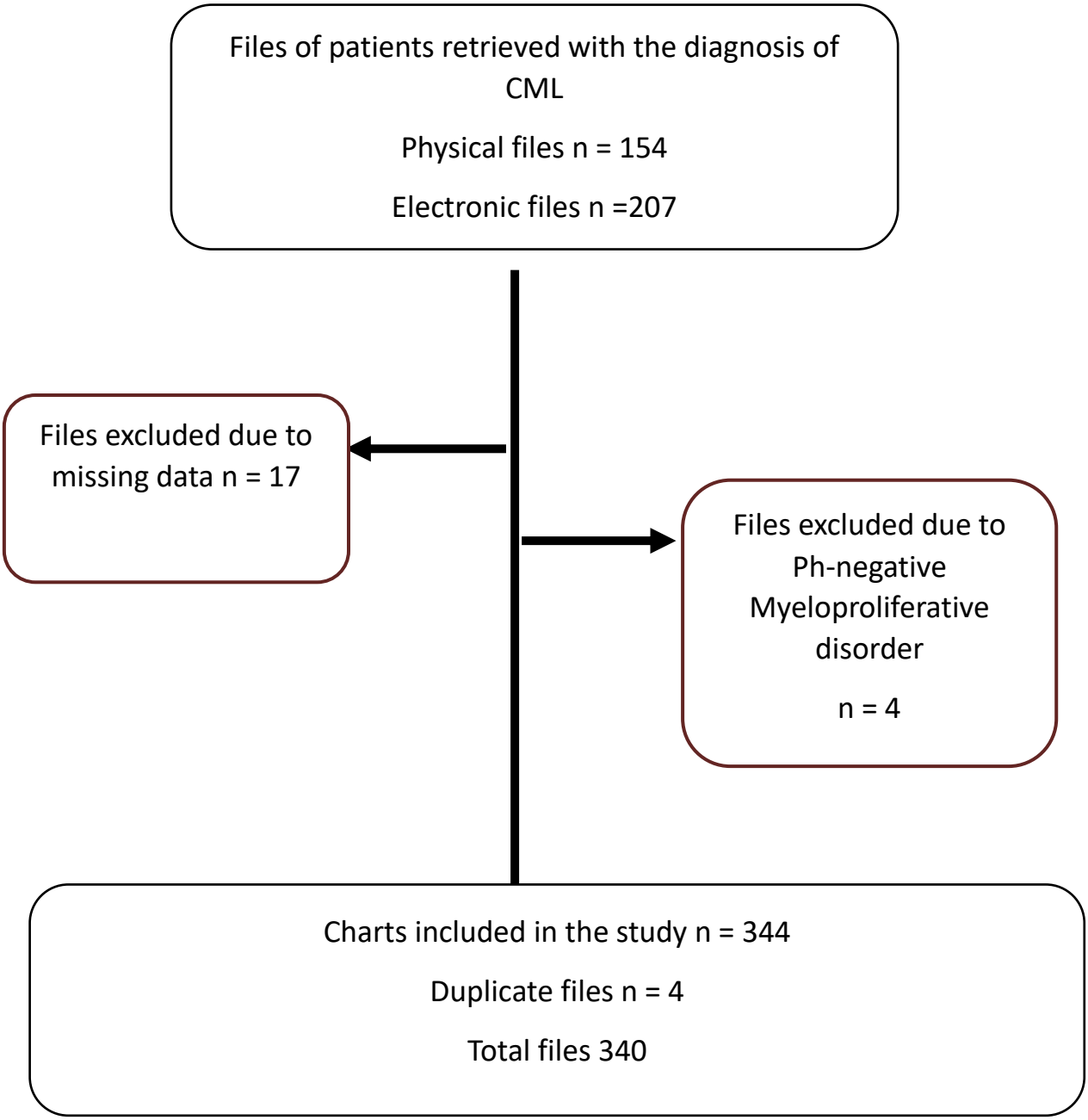


Figure 2: Flow chart for patient recruitment into the study

Flow chart for patient recruitment into the study. Of the 361 patients' files retrieved, 340 patients with CML diagnosis between 2015-2023 were finally included in the analysis. CML, chronic myelogenous leukemia; *n*, number

3.1 Social demographic characteristics and distribution of patients diagnosed with CML in Tanzania by place of residence

In the cohort of 340 patients, gender distribution for males was 53.2% (181/340) with a male-to-female ratio of 1.3:1 showing a slight male predominance. The mean age at diagnosis for CML was 38.5 years. In this cohort, the youngest patient was 4 years old while the oldest was 83 years old at diagnosis. The majority of the patients were younger than 50 years, which was represented by 77.1% (262/340), in which 31.8% (108/340) of the patients resided in Dar es Salaam. Most patients were employed or self-employed 73.8% (251/340), however only 29.1% (99/340) had health insurance. Additionally, 2.4% (8/298) of the patients were HIV positive (Table 1).

The regions out of Dar es Salaam that had a higher distribution of CML cases were Morogoro, Dodoma, Tanga and Mbeya. (Figure 2)

Table 1: Social demographic characteristics (n=340)

Variable	Frequency	Percentage
Gender		
Male	181	53.2
Female	159	46.8
Age group		
Below 18	24	7.1
18-29	72	21.2
30-39	83	24.4
40-49	83	24.4
50-59	51	15
60 and above	27	7.9
Mean (SD)	38.5	
Occupation		
Employed/Self employed	251	73.8
Unemployed	74	21.8
undocumented	15	4.4
Insurance status		
Un-insured	241	70.9
Insured	99	29.1
Location		
Dar es Salaam	108	31.8
Outside DSM	232	68.2
HIV status		
Negative	290	85.3
Positive	8	2.4
undocumented	42	12.3

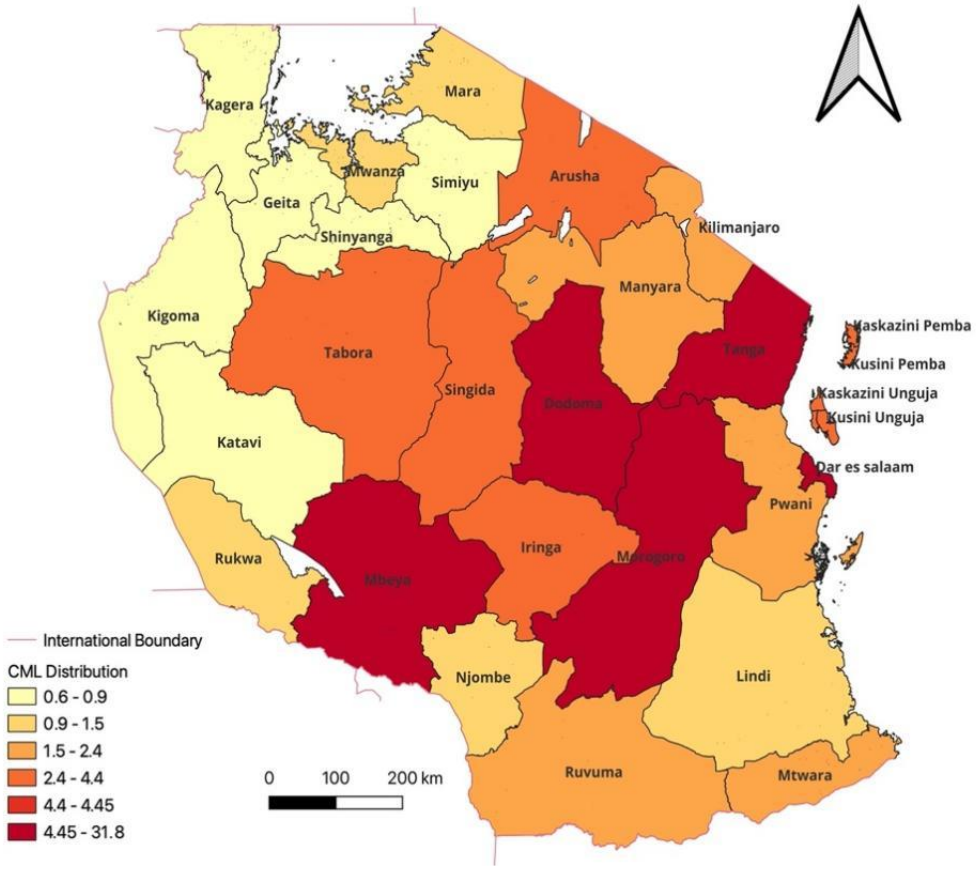


Figure 3: Distribution of CML patients in Tanzania by place of residence(n=340)

3.2 Patterns and changes in number of new CML cases at ORCI between 2015 to 2023

From the data collected, the number of new CML cases has been gradually increasing from 2015 to 2023 with an upward trend. The Chi-squire test for trend was used to estimate the increase in number of new patients, where for every year there was approximately 4 more new CML patients. (Figure 4)

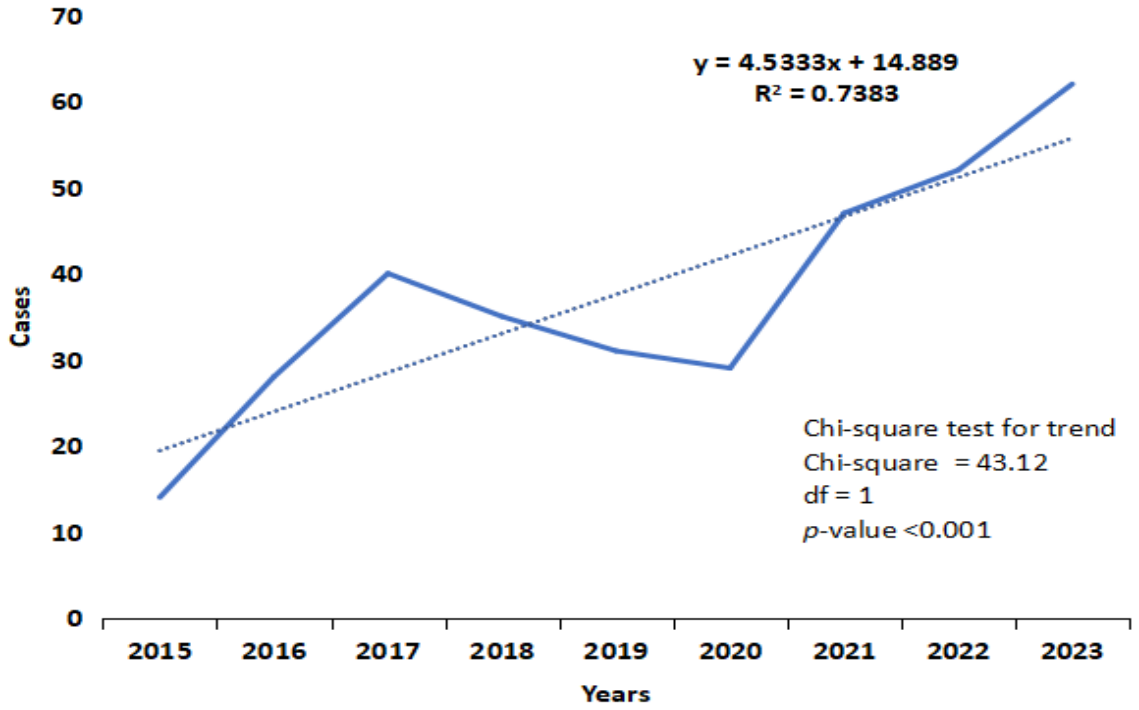


Figure 4: The patterns and changes in number of new CML case at ORCI between 2015 to 2023

3.3 Clinical characteristics of patients with Chronic myeloid leukaemia

Majority of patients at the clinic presented with ECOG 1 performance status at the initial evaluation 64.1% (218/340). Most common symptoms of these patients were anemia 98.2% (334/340), early satiety 93.8% (319/340), abdominal distension 93.5% (318/340) and fever 72.1% (245/340). Additionally, some patients had rare symptoms at diagnosis such as priapism, bleeding tendencies, hearing loss, bone pain and joint pain (Table 2).

Table 2: Clinical characteristics of patients with Chronic myeloid leukaemia (n=340)

Variable	Frequency	Percentage
ECOG		
0	15	4.4
1	218	64.1
2	87	25.6
3	20	5.9
Symptoms of anemia		
Yes	334	**98.2**
No	6	1.8
Bleeding tendency		
Yes	6	1.8
No	334	98.2
Comorbidity		
Yes	42	12.4
No	298	87.6
Fever		
Yes	245	**72.1**
No	95	27.9
Abdominal distension		
Yes	318	**93.5**
No	22	6.5
Early satiety		
Yes	319	**93.8**
No	21	6.2
Spleen size (median)	18cm	
Other symptoms		
Bleeding tendency	**14**	
Hearing Loss	**6**	
Bone and joint pain	**8**	
Priapism	**4**	

Majority of the 261 patients who had bone marrow results available were diagnosed in Chronic phase of CML which was 90.4% (236/261). Accelerated phase and Blast Phase was represented by 7.3% (19/261) and 2.3% (6/261) respectively. (Table 3)

Table 3: CML phases at diagnosis (n=261)

PHASE	Number of patients	Percentage
CHRONIC PHASE	236	90.4%
ACCELERATED PHASE	19	7.3%
BLAST PHASE	6	2.3%

3.4 Laboratory characteristics of patients with Chronic myeloid leukemia

Laboratory tests play a crucial role in the diagnosis, risk assessment, treatment decision, and monitoring of patients with CML, ultimately leading to better outcomes. The median White blood cell count at presentation for 288/340 patients was 240.3 k/µl, with 50% of patients having WBC between 142-240.3 k/µl. The median Absolute Neutrophil count (ANC), Absolute Leukocyte count (ALC) and Absolute Basophil Count (ABC) were $178.3*10^9$/L,$12.3*10^9$/L and $3.9*10^9$/L respectively. The median spleen size was 18cm with 25% of the patients presenting with massive splenomegaly. (Table 4)

Table 4: Patients lab characteristics and spleen size

Variable	Median	25% quartile	75% quartile	n
WBC (k/µl)	240.3	142	364	288
ANC (k/µl)	178.3	93.2	274	277
ALC (k/µl)	12.3	6.7	22.4	256
ABC (k/µl)	3.9	1.3	8.5	254
HB (g/dl)	8.2	6.7	9.4	286
Platelets (k/ul)	309.6	198	483	286
Spleen size (cm)	18	16	20	275

3.5 Treatment received by the CML patients from 2015 to 2024

Almost all patients used Imatinib initially as the first line of treatment, however, 29.2% (69/235) of the patients were changed to subsequent TKIs such as Nilotinib, Dasatinib, Bosutinib and Ponatinib as a result of poor molecular response, drug side effects and drug resistance.

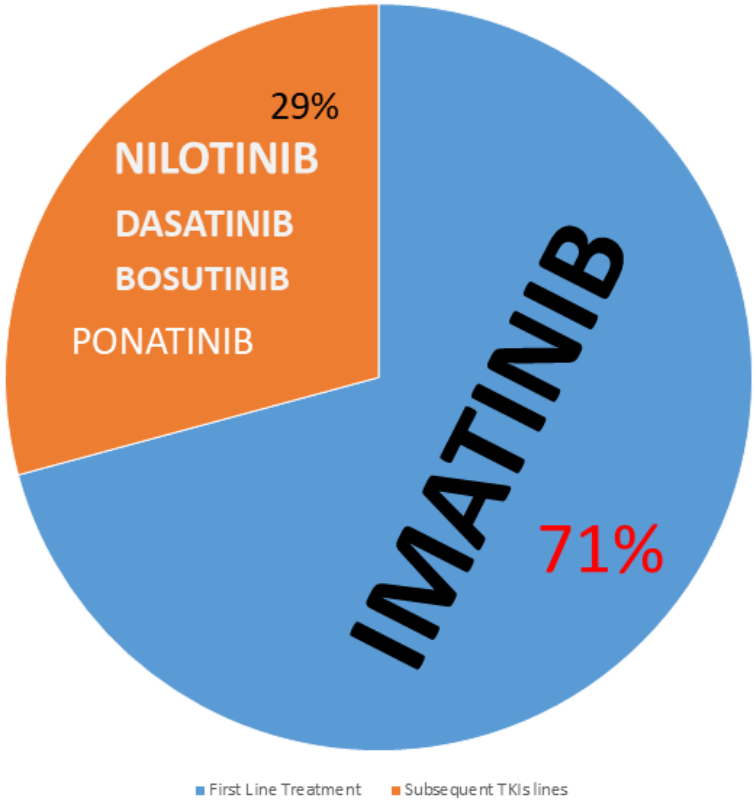


Figure 5: Treatment received by the CML patients from 2015 to 2024 n =235

3.6 Survival outcomes for patients treated for Chronic myeloid leukaemia who attended ORCI between 2015 to 2023

Results from 340 patients analyzed have shown the five-year survival of CML was 90.6% with censoring and 79.8% without censoring which only included patients diagnosed between 2015 to 2019. This was done so as to give a fuller picture of survival outcomes, allowing for better interpretation and application of survival analysis **obtained.** . Additionally, one-year and three years survival outcomes were 98.8% and 94.7%respectively.

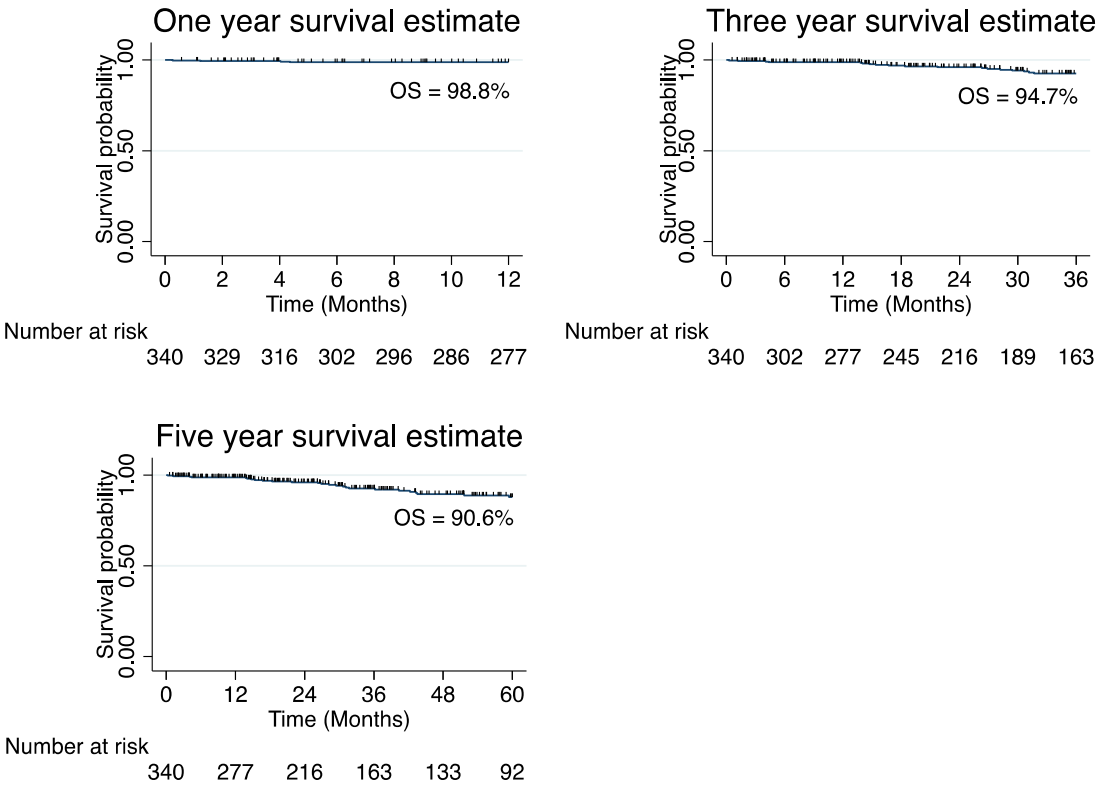


Figure 6: One-year, three-year and five-year overall survival with censoring of patients diagnosed with Chronic myeloid leukemia from 2015 to 2023

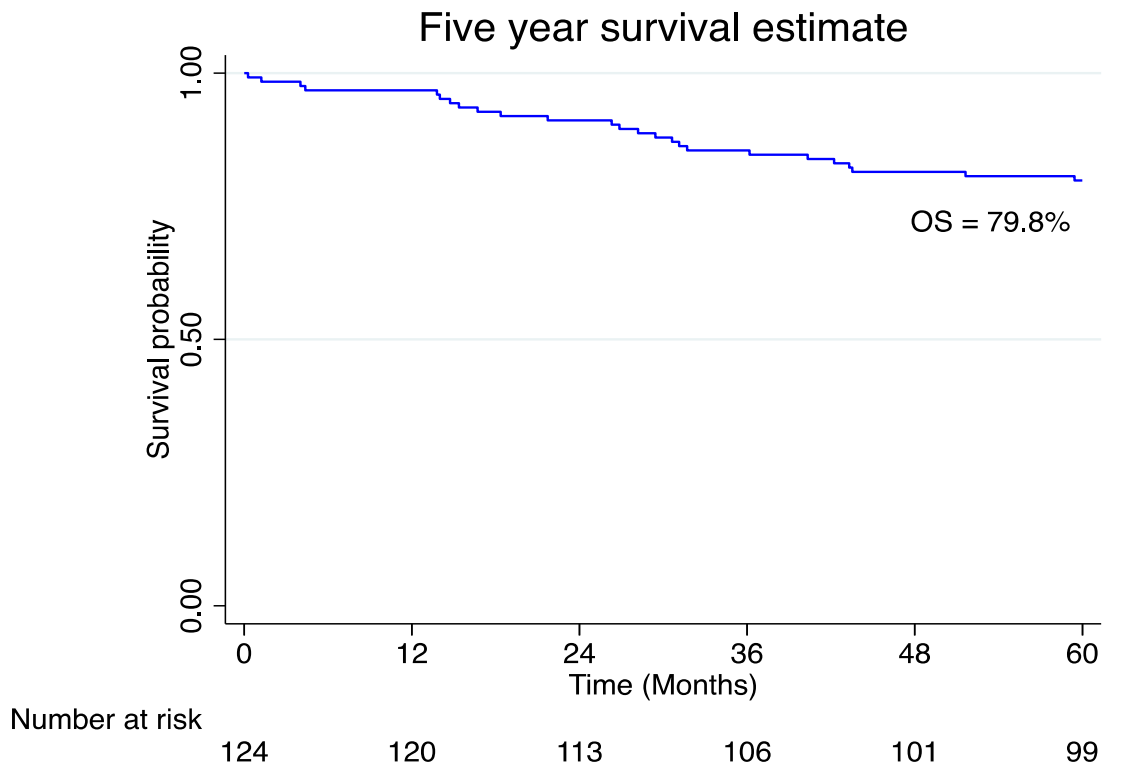


Figure 7: Five-year survival estimate without censoring for patients diagnosed with CML(2015-2019)

3.7 Survival analysis by CML phase

Survival analysis by CML phase has shown patients in the Blast phase had a poorer outcome compared to those patients who were diagnosed with CML in accelerated and chronic phases, however, the difference in survival was not statistically significant(p-value=0.065).

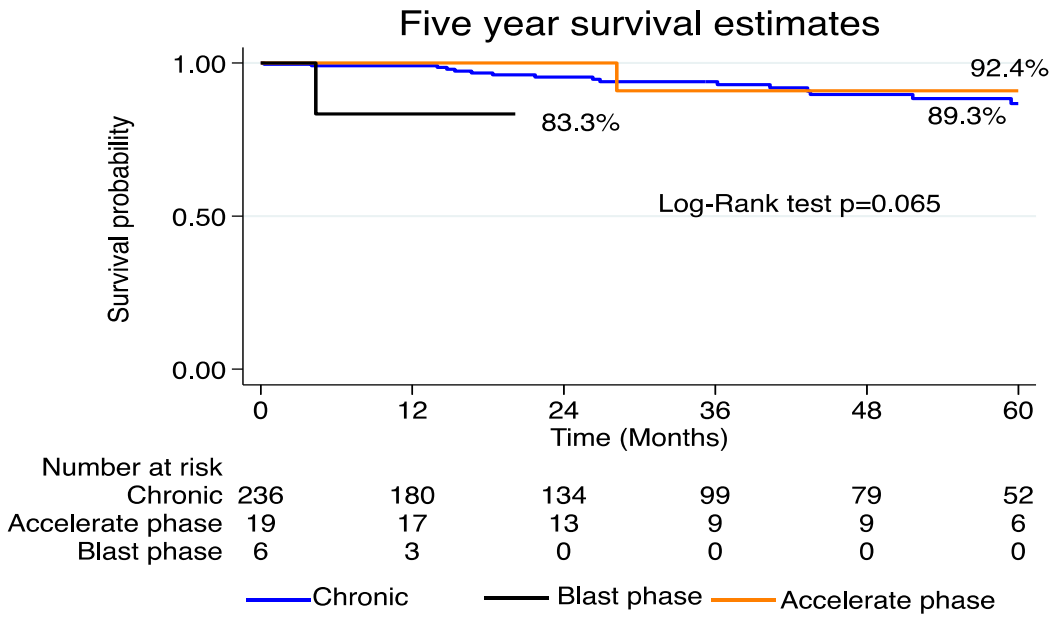


Figure 8: Five-year overall survival of patients diagnosed with Chronic myeloid leukemia by CML phases

3.8 Factors associated with survival among patients treated for Chronic myeloid leukaemia

The table detailing factors associated with survival in CML included variables like gender, age at diagnosis, occupation, insurance status, place of residence and laboratory characteristics. Multivariable Cox Regression analysis was performed to investigate the association of CML survival with these variables. There was a statistically significant association between the age at diagnosis of the patient and CML survival with the adjusted hazard ratio(aHR) of 0.93(0.87-1) with a p-value of 0. 037. This can be interpreted as for every increase in age there is a 7% less risk of death from CML. Absolute Monocyte (AMC) at diagnosis had an adjusted hazard ratio of 1.05(1.02-1.07) with a p-value less than 0.001, signifying, for every increase in AMC at diagnosis, there is a 5% risk of death from CML. The percentage of blast was also found to be statistically significant when associated with survival in the multivariate Cox regression analysis, with aHR of 1.06(1.01-1.11), p-value 0.012.

Table 5: Univariate and Multivariate analysis

Variable	cHR (95% CI)	*p*-value	aHR(95% CI)	*p*-value
Gender				
Male	Ref		Ref	
Female	1.12(0.57-2.24)	0.737	1.62(0.48-5.49)	0.442
Age	0.99(0.96-1.01)	0.274	0.93(0.87-1.00)	**0.037**
Occupation				
Employed	Ref		Ref	
Not documented	3.92(1.50-10.26)	0.005	6.18(0.51-75.04)	0.152
Self employed	0.75(0.28-1.97)	0.559	1.00(0.10-9.91)	0.998
Unemployed	0.71(0.21-2.35)	0.575	0.31(0.02-5.18)	0.415
Insurance status				
Un-insured	Ref		Ref	
Insured	1.85(0.71-4.79)	0.205	3.50(0.30-40.90)	0.318
Location				
Dar es Salaam	Ref		Ref	
Outside DSM	0.93(0.45-1.89)	0.831	1.07(0.30-3.88)	0.916
WBC	1.00(1.00-1.00)	0.484	1.01(1.00-1.01)	0.191
ANC	0.99(0.99-1.00)	0.092	0.99(0.98-1.00)	0.085
ALC	0.99(0.98-1.01)	0.686	0.99(0.97-1.01)	0.268
AMC	1.02(0.99-1.06)	0.165	1.05(1.02-1.07)	**<0.001**
Hemoglobin	0.95(0.80-1.13)	0.562	1.13(0.81-1.57)	0.484
Platelets				
Below normal	1.54(0.64-3.75)	0.336	1.70(0.41-7.00)	0.461
Normal	Ref		Ref	
Above normal	0.68(0.26-1.79)	0.441	1.18(0.34-4.17)	0.794
ABC				
Normal	Ref		Ref	
Above normal	1.01(0.43-2.38)	0.989	0.78(0.23-2.58)	0.678
CML phase				
Chronic	Ref		Ref	
Accelerate phase	1.10(0.26-4.59)	0.894	0.76(0.11-5.26)	0.782
Blast phase	8.28(1.02-66.99)	0.047	8.52(1.20-60.43)	**0.032**

CHAPTER FOUR

4.0 DISCUSSION

According to our data, the number of new patients attending ORCI's CML clinic increased linearly between 2015 and 2023, with a dip in 2019 and 2020 (Fig. 4). This decline in the linear trend of the number of new CML cases occurred during the COVID-19 pandemic, when regular hospital services were disrupted, resulting in fewer diagnoses. In addition, individuals were likely reluctant to seek care because they were afraid, they would contract COVID-19. The Chi-square test for trend was used to estimate the increase in the number of new patients, where for every year, there were approximately 4 more new CML patients. A survey with 111 doctors from 46 different countries found that, fewer patient cases were authorized for treatment in 2019 (2,902 cases versus 2,604 in 2020)(37). This shows that the pandemic caused a major disruption in healthcare services, which may have led to a decrease in the number of new CML diagnoses. While raw data can be used to analyze CML trends at a basic level, incidence and prevalence rates offer the required context and detail to accurately estimate the burden of disease, comprehend risk factors, and successfully direct public health initiatives.

Since the number of new cases of CML has been relatively consistent worldwide(5), the annual increase in this cohort can be accounted for by the advancement of diagnostic hematological services across the country and possibly due to population growth. The importance of healthcare access, socioeconomic characteristics, and lifestyle-related risk factors is highlighted by the divergent patterns in CML incidence between high-income and low/middle-income nations(5). Countrywide, only ORCI and KCMC hospitals offer free medications donated by the Max Foundation, this creates the need for healthcare stakeholders to find the solution for more reliable availability of affordable treatment across the country.

From the 340 patients, there was a gender distribution of 53.2%(181) male and 46.8%(159) female, with a male-to-female ratio of 1.3:1 showing a slight male predominance which is similar to other studies(12,16,17). The mean age at diagnosis for CML was 38.5years which is similar to low- and middle-income countries(19,38) however, compared to high-income countries the median age of diagnosis is about 57 years , where patients older than 70years

make up more than 20% and children and adolescents less than 5%(39). Conversely, in this cohort, children and adolescents account for 7.1% of the total number of patients analyzed in the study, whilst patients over 60 years of age make up just 7.9% (27). The majority of the patients were younger than 50 years which represented 77.1% (262) of all patients. Compared to populations in Western nations, those in East Africa typically experience CML at a younger age. The median age for CML diagnosis in East Africa, according to several studies, is between 39 and 41 years (19,40,41). Tanzania and other East African nations have a population that is typically younger, with a median age of about 18 to 20 years old. This leads to a greater percentage of CML patients being younger than 50 years. Given that hematological cancers generally arise at younger ages in the African population than in Western countries, genetic factors like the Philadelphia chromosome and BCR-ABL variants, in addition to environmental factors like nutrition, socioeconomic status, and exposure to toxins, are important in understanding why CML is diagnosed at a younger age in low-income countries(40,42). Younger individuals with CML, especially adolescents and young adults, may have more aggressive disease characteristics, including low hemoglobin levels, greater white blood cell counts, and larger spleen sizes(43). Additionally, younger CML patients tend to have lower rates of optimal treatment responses, potentially due to poorer adherence, and may face a slightly higher risk of disease progression(44).

The geographical location distribution showed 31.8% (108) of patients resided in Dar es Salaam and 68.2%(232) outside Dar es Salaam with the majority coming from Morogoro, Dodoma, Tanga and Mbeya regions(Fig3). This can be explained by the proximity of these regions to Dar es Salaam and the presence of referral institutions such as Benjamin Mkapa Hospital in Dodoma and Mbeya Zona Referral Hospital where hematology and other specialized services are offered. However, these hospitals do not offer a similar program to the one funded by the Max Foundation, which provides free medications to CML patients.

.Almost all patients used Imatinib initially, as the first line of treatment. However, of the 235 patients who are still active members of the hematology clinic at ORCI,29.2% were changed to subsequent TKIs such as Nilotinib, Dasatinib, Bosutinib and Ponatinib due to different reasons such as poor molecular response, drug side effects and drug resistance among others. A USA database study that included 260 patients reported that about 28% of the patients had to change from their initial drug to another TKI (45)which is similar to our findings. Patients may need to switch from one TKI to another if they develop resistance or

intolerance to the initial treatment however, access to TKIs may be limited. Patients may be stuck on a less effective first-generation TKI like imatinib, without the option to switch to a more potent second-generation TKI like dasatinib or nilotinib. Additionally, CML Patients may encounter treatment interruptions owing to medication stockouts, which could result in a loss of response and the progression of the disease. Resistance Testing for BCR-ABL1 mutations such as the T315I mutation to determine the reasons for treatment failure is also limited in Tanzania therefore, relying on the clinician's experience in managing treatment failure Across all patient populations, switching between TKIs does not always result in statistically significant gains in OS or progression-free survival (PFS)(46).

Kaplan-Meier curves were used to estimate 1,3 and 5-years survival. Censoring was used to account for incomplete information for patients whose exact time of death was unknown and for patients who were lost to follow up. Results from 340 patients analyzed has shown the five years survival of CML is 90.6%, which is comparable to high income countries. Additionally, analysis of 1 and 3years survival was 98.8% and 94.7%respectively. Umeh et al. revealed that ,the one-, three-, and five-year survival rates for all CML patients who participated in the GIPAP program, which involved 93 countries between 2001 and 2014, were 96%, 92%, and 90%, respectively(25) which is similar to our findings. The five-year survival of our cohort is high and comparable to high-income countries(47,48). This demonstrates that CML patients at ORCI do as well as patients in high-income countries despite the challenges of providing cancer care in settings with limited resources with the majority of the patients without health insurance. When survival analysis was done excluding all censored patients, remaining with 124 patients diagnosed between 2015 to 2019(fig7) the 5-year survival dropped to 79.8%. However, this smaller sample size has potential bias, lower statistical power, and lacks generalizability.

In the Multivariable Cox Regression analysis there was a statistically significant association between the age at diagnosis of the patient and the CML survival with the adjusted hazard ratio(aHR) of 0.93(0.87-1) with p-value of 0.037, interpreted as, for every increase in age at diagnosis there is a 7% less risk of death from CML. This contradicts other studies especially pre-Imatinib era, where it revealed that the prognosis for younger CML patients is better than that of older ones(49).The reason could be due to the young CML patients who are the majority in this cohort with 52.7%(179) below the age of 40years with the mean age of 38.5 years, who according to studies, present with a more aggressive disease at diagnosis with

poor prognostic indicators(50,51) compared to the older patients. Some patients visit medical facilities late ,with severe symptoms due to delay in diagnosis leading to death even before initiation of TKIs . Genetic factors may also be in play, as a study from Surveillance, Epidemiology, and End Results (SEER Stat) database done between 2002 and 2008 have suggested that young women of African descent tend to have lower relative survival rates compared to young Caucasian women in the post-imatinib era(52).However the confidence interval (CI) of 0.87-1.00 which includes 1 ,implies that the findings are not statistically significant.

Absolute Monocyte count (AMC) at diagnosis was also found to be statistically significant associated with survival with aHR of 1.05(95% CI ,1.02-1.07), indicating an increased risk of mortality with the increase in AMC at diagnosis. Monocytosis does not normally correlate with an increased risk of CML mortality. A rare variant p190 BCR-ABL which is found in about 2% of cases of CML worldwide(53–55), has been associated with monocytosis and resistance to Imatinib, however in our cohort we can cannot affirm if this variant is present among our patients. Spurious monocytosis can result from erroneous counting of other blood cells as monocytes in hematology analysers, this can also explain the uncommon association of CML survival with AMC at diagnosis (56).

The percentage of blasts at diagnosis was also found to be statistically significant when associated with CML survival, with aHR of 1.06(95%CI,1.01-1.11), p-value 0. 012.The percentage of blast is used to determine the CML phase, and it is the most important prognostic factor for CML survival. A study by Lauseker et al compared patients with more than 30% blasts to those with 20-29% blasts, the hazard ratio was 1.32, indicating a high risk of dying from CML with an elevated blast percentage above 30%(57).

Among the challenges we faced while conducting this study, were the lack of hematological data and other information such as spleen size , and liver size among others when the patient is newly diagnosed. Additionally, it is difficult to track patients' molecular response due to irregularity in the frequency of monitoring molecular response. The lack of high-quality clinical and physical examination data was also a limitation in this study. Lastly, loss to follow-up also affected survival analysis.

This study is among the first studies in Tanzania that estimated the 5-year survival of CML using a significantly large sample size.

CHAPTER FIVE

5.0 CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

There is an increase in number of new CML patients annually in Tanzania, likely due to improved diagnostics and decentralized services. Younger patients predominate with the mean age of 38.5 years at diagnosis, highlighting the socioeconomic impact. The 5-year survival is 90.6%, however, challenges persist in the sustainability of the treatment program.

5.2 Recommendations

There should be an improvement in services to cater for increasing number of new CML patients including genetic testing to assess the young age at presentation in our setting and also to assess how molecular and hematological responses influence overall survival. Adequate recording of new patients' laboratory tests when referred to ORCI and accurate patients' information and contacts documentation to aid follow up is also recommended.

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APPENDICES

Appendix I: Data Collection Tool

Age:

Sex:

Residence:

Referring institution:

Date of admission:

Comorbidity:

BMI:

ECOG:

Sokal score

Phase of CML

Blast

Accelerated

Chronic

Presenting Signs

Petechiae/Purpura

Lymph node enlargement

Splenomegaly

Hepatomegaly

Pallor

Other:

Presenting Symptoms

Fever

Headache

GBW/Fatigue

Palpitations

Early satiety

Bone pain
Other:

Mode of diagnosis
Morphology
BCR ABL ratio

Date of BMA and trephine biopsy:
Percentage of blasts:

CBC
WBC
ANC
ALC
AMC
ABC
AEC
Hb

PLT

HIV(ELISA)

Number of transfusions
PRBCs
Platelets

Treatment regimen
Imatinib
Nilotinib
Ponatinib
Dasatinib

Other treatments:

Survival outcome

Alive Dead Unknown status

If dead

Date of death

Cause of death

Appendix II :Fomu ya kukusanya taarifa za utafiti

Umri:

Jinsia:

Makazi:

Hospital anakotokea:

Tarehe ya kulazwa/kuhudumiwa

Magonjwa mengine ambatanishi:

BMI:

ECOG:

Hatua ya ugonjwa

Blast

Accelerated

Chronic

Dalili za awali za mgonjwa

Kuvilia damu

Kuvimba matezi

Kuvimba bandama

Kuvmba ini

Kupauka kwa kupungukiwa kwa damu

Homa

Kichwa kuuma

Kuchoka

Kuongezeka kwa mapigo ya moyo

Kushiba kwa haraka

Maumivu ya mifupa

Dalili nyingine (ambazo hazija ainishwa hapo juu)

Jinsi ugonjwa ulivyo gundulika

Kwa kutumia mofolojia

Kwa kutumia BCR-ABL ratio

Tarehe ya kipimo cha Uboho

Asilimia ya seli za blast:

CBC

WBC

ANC

ALC

AMC

ABC

AEC

Hb

Hct

PLT

VVU

Tiba iliyotumika

Imatinib

Nilotinib

Ponatinib

Dasatinib

Tiba nyingine:

Hali ya Mgonjwa kwa sasa (zungushia jibu)

Yupo Hai Amefariki Haijulikani

Kama amefariki

Tarehe ya kifo:

Sababu ya kifo:

Appendix III: Ethical clearance



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

MUHAS-REC-12-2023-1999 Kelvin Mbelekwa
College of Medicine MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: CHRONIC MYELOID LEUKEMIA IN TANZANIA: CLINICAL PROFILE AND FIVE-YEAR SURVIVAL

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 observational cohort study is to determine sociodemographic profiles, clinical characteristics, survival and changes in the annual incidence of CML 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-%2015134.pdf and in the MUHAS archives.

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/.



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

Appendix IV: Introduction letter

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/T.23/2021

10th January 2024

The Executive Director,
Ocean Road Cancer Institute,
P.O. Box 3592,
DAR ES SALAAM

Re: INTRODUCTION LETTER

We would like to inform you that the bearer of this letter is Kelvin Mbelekwa with Reg. No. HD/MUH/T.23/2021 is a student at Muhimbili University of Health and Allied Sciences (MUHAS) "pursuing MMed. Clinical Oncology.

As part of his studies, he will be doing an elective research titled: "**Chronic Myeloid Leukemia in Tanzania: Clinical Profile and Five Year Survival**" he is being supervised by Dr. Salum Lidenge from MUHAS and Dr. Hamisa Iddy from ORCI.

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

Kindly provide him the necessary assistance to facilitate the conduct of his research.

We thank you for your cooperation.

Ms. Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES

c: Kelvin Mbelekwa

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