ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

Clinical profile, treatment outcome and predictors of treatment outcome of Chronic Lymphocytic Leukemia (CLL) patients at Tikur Anbessa Specialized Hospital

A three-year retrospective study

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Abbreviations

AAU……....Addis Ababa University
AIHA……....Autoimmune Hemolytic Anemia
ALC…….Absolute Lymphocyte Count
ALP……..Alkaline phosphatase
ANOVA……..Analysis of Variance
AST……..Aspartate Transaminase
BLCM……..Below Left Coastal Margin
BR……Bendamustine-Rituximab
BRCM…….Below Right Coastal Margin
BM……. Bone Marrow
BTKi……..Bruton Kinase Inhibitors
CD……. Cluster of Differentiation
CLL……Chronic Lymphocytic Leukemia
CLL-IPI……..Chronic Lymphocytic Leukemia-International Prognostic Index
CML……...Chronic Myelogenous Leukemia
COVID 19……..Corona Virus Disease of 2019
CR……..Chlorambucil-Rituimab
CR……..Complete Remission
CVP……Cyclophosphamide, Vincristine, Prednisolone
DAT……Direct Agglutination Test
DVT……...Deep Venous Thrombosis
FCR……Fludarabine, Cyclophosphamide, Rituximab
FR……...Fludarabine-Rituximab
FISH……...Florescent In-situ Hybridization
FMoH…….Federal Ministry of Health
ITP…….Immune Thrombocytopenia
Hb……..Hemoglobin
HBsAg……...Hepatitis B Surface Antigen
HCV Ab……Heptitis C Virus Antibody
HF……..Heart Failure
HIV……Human Immune-deficiency Virus
IGHV…… Immunoglobulin Heavy Chain
JVP……Jugular Venous Pressure
LDH……...Lactate Dehydrogenase
LDT……Lymphocyte Doubling Time
MRD…….. Minimal Residual Disease
MRN…….. Medical Record Number
PFS…… Progression Free Survival
PR……...Partial Remission
PD……...Progressive Disease
R-CVP……Rituximab, Cyclophosphamide, Vincristine, Prednisolone
SD……...Standard Deviation
SEER……. Surveillance Epidemiology and End Results
TASH……Tikur Anbesa Specialized Hospital
TLS……Tumor Lysis Syndrome
WBC……..White Blood Cell

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Abstract

Background

Chronic Lymphocytic Leukemia (CLL) is the most prevalent type of leukemia worldwide. So far there are only few studies conducted in this area in Ethiopia. Understanding of the current clinical presentation as well as outcome of treatment in CLL patients is relevant in improving diagnostic as well as treatment modalities of this disease in developing countries such as Ethiopia.

Objective

The main objective of this study is to describe the clinical profiles and treatment outcomes of Chronic Lymphocytic Leukemia (CLL) patients at Tikur Anbessa Specialized Hospital.

Methods

A retrospective cross sectional design was used to conduct the study at Tikur Anbessa Specialized Hospital from September 1, 2021 to December 31, 2022. Structured questionnaire was used to collect data from electronic medical recording system of all adult Chronic Lymphocytic Leukemia (CLL) patients seen at Hematology clinic from September 2019 to August, 2022. Descriptive as well as correlation analysis were done using the software Statistical Package for the Social Science (SPSS) data editor version 25 .0.

Result

There were a total of 169 Chronic Lymphocytic Leukemia (CLL) patients included in the study. The male-to-female ratio was 1.91:1. The mean age at diagnosis was 57 years. Majority of patients were from the capital Addis Ababa. The commonest presenting symptom was swelling at lymph node site which was found on 58.4% and the commonest presenting sign was palpable lymphadenopathy in 74%. The commonest laboratory finding was leukocytosis (91.5%). Majority of patients had Rai stage 2 disease (34.7%) followed by Rai stage 1 disease in 24%. Only 33% of the patients required CLL directed therapy with the commonest indication for treatment being Rai stage 3 or 4 disease. The commonest first line regimen used was BR regimen. Total response rate to first line regimen was 76.1%. The relapse rate among responders was 57.1%. The lost to follow up rate was very high, 55.6% and the proportion of confirmed death was18.3% from the whole cohort. Age, sex and treatment regimen were among the factors affecting treatment response and sex was the major factor affecting relapse rate and progression free survival with female patients having better response, lower risk of relapse and longer progression free survival than males. Overall survival was affected only by age with patients younger than 50 years having better overall survival.

Conclusion

The clinical presentation of patients with CLL in our set up is similar with most centers worldwide but with younger mean age at presentation. The proportion of advanced disease seems to have lowered compared from previous findings. Response to therapy are comparable with other similar set ups. Age, sex and type of regimen are major factors affecting response to treatment.

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1. Introduction

1.1. Background

Chronic lymphocytic leukemia (CLL) is the most prevalent subtype of leukemia in the western world, causing a substantial health burden on patients and society. It is very rare before 45 years of age and uncommon before 65 years of age. The estimated survival at 5 years after diagnosis is 81.7% which explains the estimated prevalence of CLL patients to increase over time. CLL is more common in men than women. In terms of racial prevalence, CLL is more common in whites compared with blacks, Hispanics or Asians.[1,2]

With regards of predisposing factors there are no strong evidences that exposure to benzene or radiation increases the risk of developing CLL. However, exposure to Agent Orange was shown to increase the incidence of CLL as was demonstrated in Vietnam war veterans.[2, 3]

In terms of the epidemiology of CLL in Ethiopia, a retrospective institutional based study published in 1996 reported 102 cases of CLL seen at Tikur Anbesa Specialized Hospital within 12 years of study duration. The mean age at diagnoses was 55.6 years which was younger than western reports and males accounted for majority of the patients with a ratio of 3.6:1. Among the patients 56% had advanced disease (Rai stage III and IV). Among those who received chemotherapy 22% had complete response and 48% had partial response.[4]

The goal of treatment in CLL is amelioration of symptoms but not cure. As relapse is inevitable in all patients and as early treatment is not associated with better survival, treatment is not recommended for all patients diagnosed with CLL unless they have indications for treatment.[5]

The standard treatment for chronic lymphocytic leukemia (CLL) has experienced a dramatic change over the last few years. Until recently, CLL was treated using chemotherapy in combination with anti-CD20 antibody-based immunotherapy. Currently, patients are mostly treated with so-called novel agents, including BTK inhibitors, Bcl-2 inhibitors and PI3K inhibitors, which are generally well tolerated but have a specific side effect profile.

In conclusion, the prevalence of CLL is raising worldwide. Similarly, diagnostic as well as treatment modalities are changing with the use of more sophisticated cytogenetic and molecular tests being used to prognosticate patients and accordingly decide on the choice of therapy. Likewise, the use of conventional chemotherapeutic agents with higher toxicity are being replaced by more targeted but expensive mode of therapy. These agents are also further prolonging PFS of patients.

1.2. Statement of the problem

The clinical features and outcome of CLL patients in Ethiopia was described by a study done at the Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, by Shamebo and Gebremedhin from January 1982 to December 1994. This study reported a total of 102 cases of chronic lymphocytic leukemia (CLL) with age range of 35-91 with a mean age at presentation of 55.6 years. In this study males were affected more with a male to female ratio of 3.6:1.[4] However this study was done almost 30 years ago and there are no recent studies looking at epidemiologic changes in clinical presentation as well us treatment outcome in the most recent years.

CLL is an indolent disease which requires long term medical follow up. This becomes a challenge to most developing countries where patients have to travel long distance to seek specialized care and the primary health facilities are not equipped with both man power and investigational gadgets to follow such patients. This makes discontinuation of medical follow up one of the common challenges seen in developing countries. This is usually due to financial constraint by most patients. For example, in the Ethiopian study by Shamebo and Gebremedhin and a study from India demonstrated that significant number of patients are lost from their follow ups.[4, 7]

The other major challenge is unavailability of diagnostic modalities such as flowcytometry and cytogenetic and molecular tests which are important in prognostication as well as treatment selection. Diagnosis of CLL in most African studies is based on morphological diagnosis. Immunophenotypic and cytogenetics tests are rarely used. This diagnostic challenge is also encountered in our setup. Majority of patients are diagnosed based of clinical presentation with bone marrow aspiration result as a confirmatory investigation. This might open a room for the misdiagnosis of other lymphoproliferative neoplasms as CLL and erroneous clinical decisions.[4, 8]

The other challenge is lack of chemotherapeutic, novel targeted agents and as well as a poor supportive care. Treatment advances in cancer usually originate in the West but their worldwide application is impeded by both financial and infrastructure constraints. The current advances in CLL recommend targeted agents like Ibrutinib and Venitoclax as a first line therapy for patients with high-risk molecular features which are very expensive. The harsh reality though is, even inconsistent availability of chemoimmunotherapy and absence of cytogenetic and molecular studies to identify these high-risk patients is a huge challenge by itself. Coming to our set up, in Tikur Anbesa Specialized Hospital, treatment of CLL patients entirely lies on chemoimmunotherapy and especially treating relapsed patients is quite a challenge [4,9,10]

However, there are success stories even in developing countries such as establishment of a comprehensive clinic for CLL at an academic center in Chandigarh, India equipped with Fluorescent in situ hybridization (FISH) for CLL prognostication, flow analysis for minimal residual disease (MRD) led to improved quality of care in CLL patients.[7]

Therefore, studies like this one will help in identifying gaps on diagnosis and treatment of specific hematologic diseases and findings will be used to come up with recommendations in order to improve diagnostic as well as treatment capacities of such centers.

1.4. Significance of the study

Chronic Lymphocytic Leukemia (CLL) is one of the common hematologic malignancies treated at Tikur Anbesa Specialized Hospital. However, little has been done so far to look into the details of the clinical presentation and treatment outcome of CLL patients treated at this center. There has been one published study done almost 30 years back reporting the clinical presentation and outcome of 102 CLL patients from Tikur Anbesa Hospital. However, a lot of changes has been made on treatment recommendation both internationally and in this specific center. Therefore, using the old study to define the clinical presentation as well as treatment outcome of CLL patients will be inappropriate.

Even though, there is no study done in the recent years the number of patients being referred from the whole country seems to be increasing at least from physicians' account. From monthly audits of cases seen at the

hematology clinic there seems to be an increase in the number of CLL and all other hematologic visits. Therefore, this new retrospective study will help in acquiring information on recent changes in the sociodemographic characteristics as well as clinical presentation and treatment outcome of CLL patients treated with current chemoimmunotherapy regimens at Tikur Anbesa Specialized Hospital (TASH) in the recent years.

It will also help identify gaps in the diagnosis such as unavailability of flowcytometry which would definitely result in misdiagnosis of some patients. Similarly, the absence of prognostic laboratory investigations such as B2-microglobulins, cytogenetic and molecular tests which would affect the therapy of CLL patients would be looked into. The other significance of this study is to evaluate the rate of response to the chemoimmunotherapy regimens commonly used in this setup. Drug unavailability is also one of the common challenges especially that of Rituximab which is actually expensive for most patients to buy from private pharmacies in time of unavailability from the hospital's pharmacy. This usually leads to treatment discontinuations and loss of follow up of patients. This study will also asses the degree of treatment interruptions and loss from follow up and assess the potential reasons for that.

This study will help as an eye opener to study specific areas of concern regarding CLL in the near future. Findings of such intricate information will help the researcher to issue evidence-based recommendation for facility upgrading with advanced diagnostics as well as ways to improve sustainable drug availability.

This study also will try to identify patients with multiple relapses and are refractory to all other regimens available. This is also another huge challenge as there are only limited options and advanced targeted therapy which are of paramount importance in such cases are lacking. Therefore, identifying the magnitude of such patients will help to notify to the concerned body to work on making novel targeted therapy available.

2. Objectives

2.1. General Objective

- To study the clinical presentations, treatment outcome and factors affecting response to treatment of patients diagnosed to have Chronic Lymphocytic Leukemia at TASH within three-year time, from September 2019-August 2022

2.2. Specific Objectives

- To describe the clinical presentation of patients with Chronic Lymphocytic Leukemia patients seen at TASH from September 2019- August 2022
- To study treatment outcome of Chronic Lymphocytic Leukemia patients seen at TASH from September 2019- August 2022
- To identify factors affecting response to treatment and survival in CLL patients

3. Methodology

3.1. Study Design

A retrospective cross-sectional design was used to study the clinical characteristics, hospital course and treatment outcomes and determinants of outcome among Chronic Lymphocytic Leukemia patients seen at TASH in three years period.

3.2. Study Area

The study area is Tikur Anbessa Specialized Hospital which is the largest governmental teaching hospital in Ethiopia located in the capital Addis Ababa. It is also a training center for undergraduate and postgraduate medical students and had produced many medical doctors, nurses, pharmacists for the past 58 years.

It is estimated that it serves up to 500,000 patients a year and has close to 700 beds. It is also an institution with the major oncology and hematology treatment centers in the country. The Internal Medicine department of TASH is one of the oldest departments and has around 100 beds. Among these around 40-42 of them are dedicated to hematology patients currently.

In addition to the in-patient service, Tikur Anbesa Hospital gives an out-patient specialty and sub-specialty services. Among this sub-specialty clinics, hematology clinic delivers its service for 1200-1500 patients monthly. Patients with benign hematologic diseases, Chronic Myeloid Leukemia (CML), CLL, Lymphoma, Multiple Myeloma and others are among the many hematologic patients seeking care at this facility.

3.3. Study Period

The study was conducted from September 1, 2021 to December 31, 2022.

3.4. Study Population

3.4.1. Source population

All patients diagnosed to have CLL and seen at hematology clinic of TASH within the three years period from September 1, 2019 to August 31, 2022 were included in the study.

3.4.2. Study Subjects

All patients diagnosed to have chronic lymphocytic leukemia and seen at the out-patient hematology clinic in TASH within the study period and who fulfilled the inclusion criteria were included.

3.4.3. Sampling Method

Since this is an institution-based study, the plan was to include all patients seen during the specified study period. Accordingly, all adult (≥18 age) patients diagnosed to have chronic lymphocytic leukemia, fulfilling the criteria and seen at TASH from September, 2019 to August 31, 2022 were included in the study.

3.5. Data Collection

3.5.1. Inclusion Criteria

- All adult patients(≥18 age) diagnosed to have chronic lymphocytic leukemia and seen at TASH from September, 2019 to August 31, 2022
- All patients had at least a confirmed morphologic diagnosis of chronic lymphocytic leukemia

3.5.2. Exclusion criteria

- Patients suspected to have chronic lymphocytic leukemia clinically but no pathologic diagnosis was made during their visits were excluded from the study.

3.5.1. Study variables

Independent variables

- Age
- Sex
- Stage of disease
- Time from symptom onset until presentation
- Laboratory findings
- Time of treatment commencement
- Comorbid conditions
- Functional status
- WBC at presentation

Dependent variables

- Time to require treatment
- Response to treatment
- Overall Survival rates
- Progression free survival
- Relapse

3.5.2. Operational Definition

- **Adult**- ≥18 years
- **Complete Remission(CR)**
    - Requires all of the following criteria:
        - Absolute lymphocyte count <4000/microL ($4 \times 10^{9/}$L).
        - No lymph nodes >1.5 cm in diameter.
        - No hepatomegaly or splenomegaly.
        - No constitutional symptoms attributable to CLL.
- **Partial Remission(PR)**
    - At least two of these criteria must be documented:
        - A decrease in the peripheral ALC by at least 50% from the level prior to therapy.

        - A reduction in previously enlarged nodes by at least 50% with no increase in the size of any single lymph node and no new enlarged lymph nodes. An increase of <25% in a lymph node <1.5 cm is not considered significant.
        - A decrease in the size of the liver and/or spleen by at least 50%.

    - One of the following hematologic parameters must be met in addition to two of the above criteria in order to qualify for a PR:
        - Platelet count ≥100,000/microL(100×10^9/L) or at least 50% improvement over baseline (if this value was abnormally low at baseline).
        - Hemoglobin concentration ≥11 g/dl (110 g/L) or 50% improvement over baseline (if this value was abnormally low at baseline) without red blood cell transfusions or erythropoietin support.
    - If only one parameter was abnormal before therapy, only one needs to improve to achieve PR.

- **Progressive disease (PD)/Relapse**
    - At least one of these criteria must be documented:
    - The appearance of a newly enlarged lymph node (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltration.
    - An increase of 50% or more in size of a previously involved site (eg, lymph nodes, spleen, or liver) measuring ≥1.5 cm.
    - An increase of 50% or more in the total circulating lymphocyte count with ALC of 5000/microL (5×10^9/L) or greater.
    - Richter's transformation documented by lymph node or other tissue biopsy.
    - Development of neutropenia, anemia, or thrombocytopenia attributable to CLL.
- **Stable disease**
    - Patients who do not meet the criteria for a complete remission, partial remission, or progressive disease, have stable disease. Stable disease is therapeutically equivalent to a nonresponse (i.e, refractory disease).

3.6. Data collection and analysis methods

All patients who are referred to as known cases of CLL and those who were diagnosed as new patients at the Hematology clinic TASH, Addis Ababa, from September 1, 2019 to August 31, 2022 inclusive fulfilling the inclusion criteria are enrolled in the study. Data was collected mainly from electronic medical records using a structured questionnaire. The out-patient log books were used to obtain medical record numbers of patients diagnosed and treated for chronic lymphocytic leukemia.

Accordingly a total of 402 patients were identified to be seen at hematology clinic with diagnosis of CLL. Among these 169 patients were confirmed to have chronic lymphocytic leukemia based on clinical features, blood counts, peripheral blood films and most importantly bone marrow examination and they were enrolled to the study. 16 patients might probably had CLL but they were seen at the clinic once or twice and they were lacking both morphologic and immunophenotypic diagnosis and they were excluded from inclusion. The rest of 61 patients had other hematologic diagnosis such as CML, ITP, DVT, lymphoma and

different types of anemia. The other 156 patients had other non-hematologic diagnosis or some I-care number were non-existent and probably were erroneously recorded on the hematology log book.

After patients fulfilling criteria were identified questionnaires were filled by trained data collectors, particularly final year medical students and interns who were well familiarized in interpreting the clinical records of patients. The cases are characterized with respect to age, sex, stage of disease, outcome of treatment and survival of patients. The data collection process was closely supervised by the principal investigator.

After data collection is complete, data was edited and coded for processing and analysis. Data processing and analysis was done manually and using the SPSS statistical software with the assistant of experienced data analyst. Result were reported using descriptive statistical methods such as frequency, percentages, tables and graphs. Association studies were done using Chi-square test for categorical variables, Spearson's Rho method for ordinal variables and ANOVA test for continuous variables. Multinomial logistic regression were also done to assess the effect of different factors on outcome. Survival analysis was done using Kaplan Meier curve with Log rank test. Level of significance was set at P-value of 0.05 or less in all scenarios.

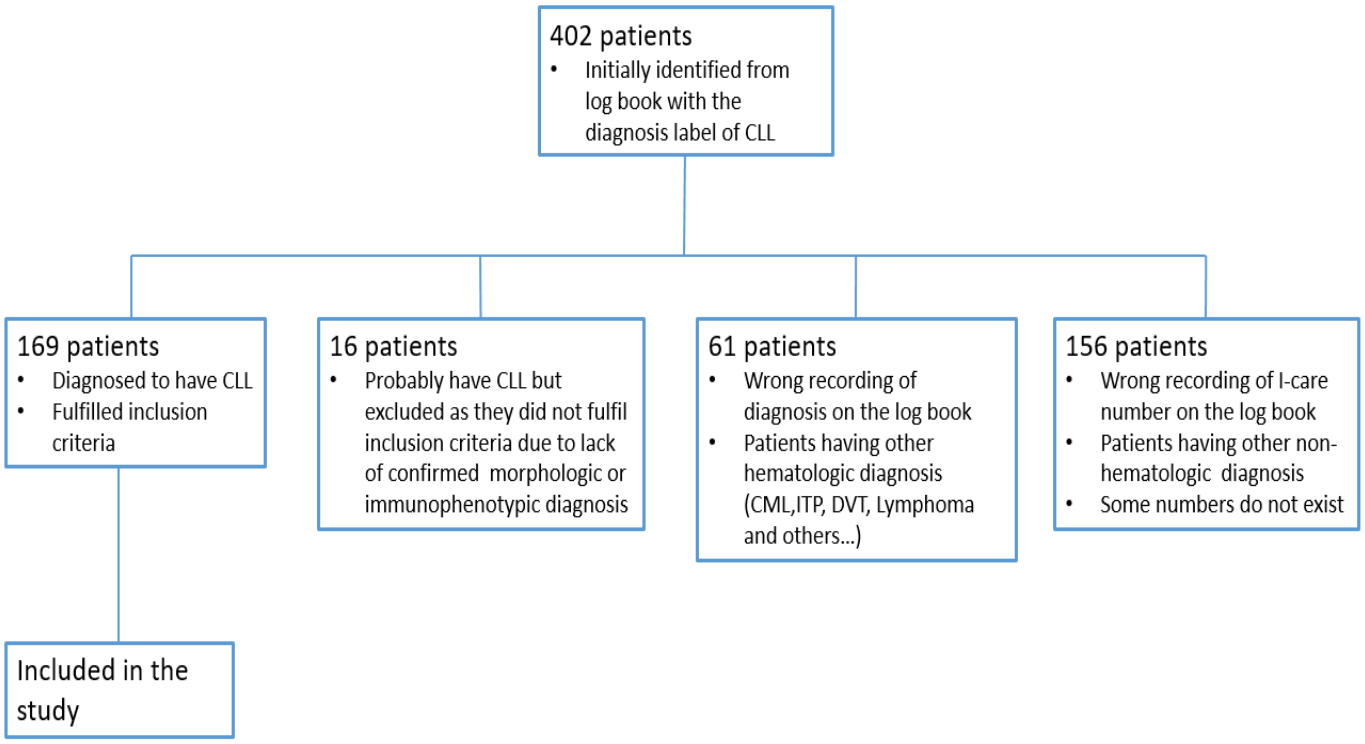

Figure 1: Sampling procedure

4. Ethical Consideration

Ethical clearance was obtained from the ethical review committee at the Department of Internal Medicine and study proposal was approved by the ethical committee which in to the College of Heath Science, Addis Ababa University before the commencement of the study.

5. Dissemination of research results

After the completion of the research, the result will be presented to the Hematology unit, Department of Internal medicine and possibly to the whole academic society of interest such as College of Health Science and AAU staffs. Finding will also be presented on annual conferences and seminars for the medical community at large.

Research findings will be sent to both national and international medical journals for publishing and it will be disseminated through internet to different medical sites. Results will also be disseminated to other teaching and non-teaching hospitals and regional health bureau in collaboration with the Federal Ministry of Health (FMoH) and other stakeholders such as professional associations.

6. Result

6.1. Socio-demographic characteristics

A total of 169 adult patients were diagnosed with CLL at Tikur Anbesa Specialized Hospital (TASH) from September 1, 2019 to August 31, 2022. Among the 169 patients 111(65.7%) were males and 58(34.3%) were females with a M: F ratio of 1.91:1. The age of patients ranged between 29 and 82 years. The median age at diagnosis was 58 years whereas the mean age at diagnosis was 57(±12) years. Majority of the patients were in the age category of 51-60.

In terms of regional distribution, majority of patients 61(36.1%) were from the capital city Addis Ababa, followed by 58(34.3%) from Oromia region, 25 (14.8%) from Amhara region and 22(13%) from SNNPR. One patient each came from Somale region, Harari region and Dire Dawa city administration.

Table 1: Socio- demographic characteristics of CLL patients

Variables	Number	Percentage
Sex		
Male	111	65.7%
Female	58	34.3%
Age Category		
≤40	14	8.3%
41-50	41	24.3%
51-60	48	28.4%
61-70	42	24.9%
71-80	21	12.4%
≥81	3	1.8%
Region		
Addis Ababa	61	36.1%
Oromia	58	34.3%
Amhara	25	14.8%
SNNPR	22	13%
Somale	1	0.6%
Harari	1	0.6%
Dire Dawa	1	0.6%

6.2. Clinical and Laboratory Findings

Among the 169 patients information on initial clinical presentation was available only for the 154 patients. Among these 11(7.1%) of them were completely asymptomatic and they were referred to TASH after routine abnormal blood count. The rest of 143 patients were symptomatic and their clinical presentations were documented. The most common presenting symptom was swelling noted at lymph node sites which was present in 90(58.4%) of patients. This was followed by presence of constitutional symptoms which was apparent in 89(57.8%), followed by symptoms of anemia which was present in 56(36.4%).
The duration of illness at the time of presentation ranged from 1 week to 364 weeks (7 years). The median duration of illness was 24 weeks (6 months). The mean duration of illness at presentation was 48.5 weeks (SD±62.2).
In terms of physical findings, the commonest physical finding was palpable lymphadenopathy which was found in 114(74%) of the patients, followed by splenomegaly which was present in 46(29.9%) of the patients with measured spleen size ranging between 2- 20 with a mean of 6.7 cm (SD±3.5) BLCM. Pallor was found in 30(19.5%) of the patients. Hepatomegaly was present in 20(13%) of the patients with measured liver size, ranging between 2-10 cm with the mean of 4.5 cm (SD±2.5) BRCM.
The details of other presenting symptoms and signs are depicted in the table below.

Table 2: Clinical presenting symptoms and signs of CLL patients

Symptoms	Percentage	Physical Findings	Percentage
Swelling at Lymph node sites	58.4%	Palpable Lymphadenopathy	74%
Constitutional symptoms	57.8%	Splenomegaly	29.9%
Symptoms of anemia	36.4%	Pallor	19.5%
Abdominal swelling	13.6%	Hepatomegaly	13%
Symptoms of infection	7.8%	Signs of HF(raised JVP/Gallop)	3.2%
Bleeding	0.6%	Fever	0.6%

The most common laboratory finding on initial laboratory examination was leukocytosis which was present in 140(91.5%) with a mean total WBC count of 111,136 cells/µl and mean lymphocyte percentage 78.9% (SD±18.1%). Anemia was present in 70(45.7%) of patients on initial presentation and among these 35 patients (22.8%) had Hemoglobin level (Hb) less than 10mg/dl. Thrombocytopenia was present in 67(44%) of patients and among these 26(17.1%) of them had platelet count below 100,000 cell/µl.

The serum LDH level ranged from 106 IU/ml to 1281 IU/ml with a median value of 270 IU/ml. The serum uric acid ranged between 1.3mg/dl and 12.1mg/dl and the median was 6.3mg/dl. The serum creatinine ranged between 0.4mg/dl and 1.6mg/dl with a median of 0.9 mg/dl. The total bilirubin level ranged between 0.08mg/dl to 2.3mg/dl with a median value of 0.6mg/dl and the direct bilirubin ranged between 0.02mg/dl and 1.2mg/dl with a median of 0.11mg/dl.
Tumor lysis syndrome (TLS) parameters were available for 101 patients only and among these there were only two confirmed cases of TLS.

Rai and Binet staging were performed for 150 patients at the time of presentation, 5 patients lacked peripheral lymphocytosis and likely presented as a small lymphocytic lymphoma patients initially. Majority of patients 52(34.7%) had a Rai stage 2 disease followed by a Rai stage 1 disease which was found in

36(24%). When Binet staging was used majority, 71(47.3%) of the patients fall in Binet B class. Details of the staging of patients are depicted on Figure 1 & 2 below.

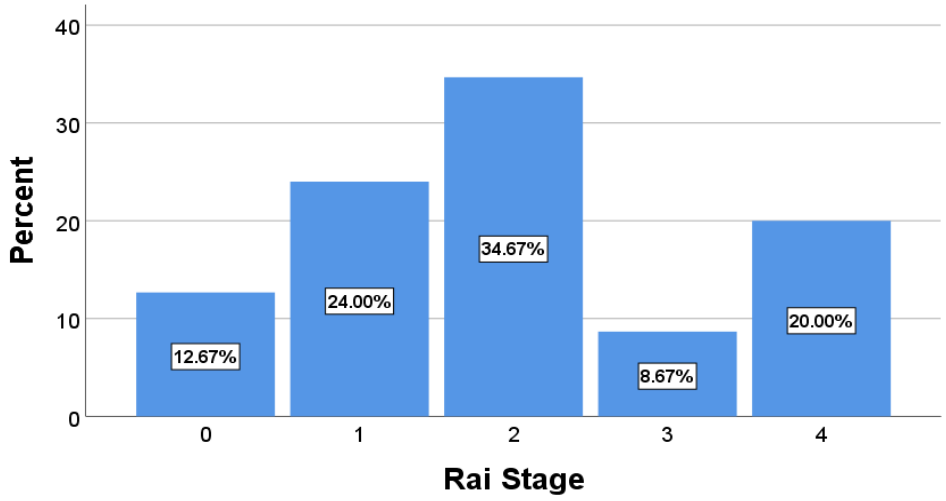

Figure 2: Rai stages of patients at presentation

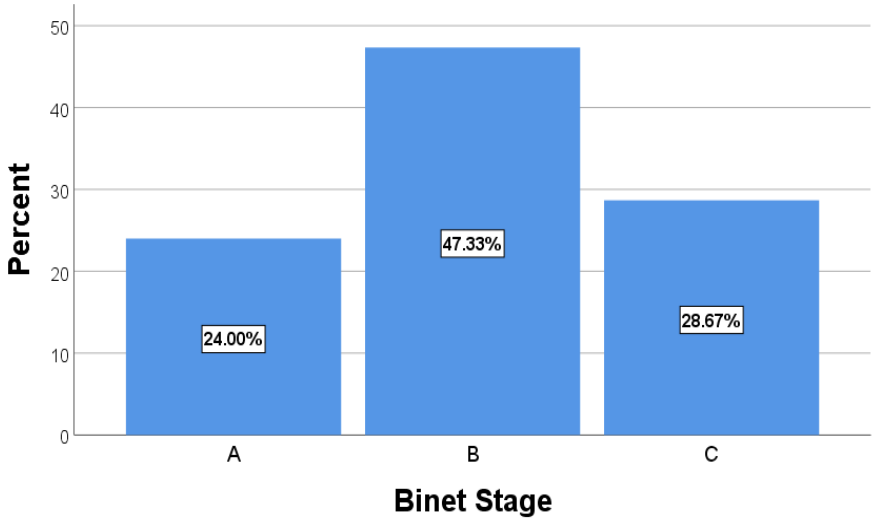

Figure 3: Binet stages of patients at presentation

With regards to the mode of the diagnosis, majority of the patients 136(80.5%) had only morphological diagnosis. About 32(19.5%) were diagnosed by combining morphology and flow cytometry. Among all patients only 3(1.7%) had cytogenetics done for prognostication.

Looking at the prevalence of concomitant comorbidities, HIV status was available for 61 patients and among these 7(4.2%) had HIV infection. Hepatitis B surface antigen (HBsAg) status was available for 108 patients and among these 6(3.6%) patients had a positive HBsAg test. HCV antibody (HCV Ab) status was available for 103 of patients and 2(1.2%) of them had a positive test. Among all patients 22(13%) had

diagnosed hypertension, 17(10.1%) had diagnosed diabetes mellitus and 7(4.1%) had known cardiac disease, dermatologic disease diagnosed by dermatologic evaluation such as (Eczema and pyoderma) were present 9(5.3%) of patients during their follow up. 6(3.6%) of patients developed Herpes zoster and another 9(5.3%) of patients were diagnosed with COVID infection during their follow up.

During the follow up period of the three years, autoimmune cytopenias associated with CLL were diagnosed in a total of 31(18.3%) of the 169 patients. Out of these, 14(8.3%) of them had clinically diagnosed isolated Autoimmune Hemolytic Anemia (AIHA), 8(4.7%) of them had isolated immune thrombocytopenia (ITP) whereas 9(5.3%) had a combination of the two. All of these patients received steroid therapy.

6.3. Treatment Status and Outcome of therapy

Regarding treatment status out of 169 patients, 59 (34.9%) of patients did not take any therapy during their follow up and they were conservatively followed. A total of 17 patients (10.1%) took only supportive therapy such as steroid and folate supplementation or a combination of both. Folic acid supplementation was given to a total of 58 patients which makes up 34.3% of the whole cohort. A total of 93 patients (55%) required CLL directed therapy at one point during their follow up. The details of the combination of therapy for patents are depicted on Table 3 below.

Table 3: Type of therapy received by CLL patients

Type of therapy	Number(Percent)
Did not take any therapy	59(34.9%)
Steroid only	4(2.4%)
Folic acid only	8(4.7%)
Steroid and Folic acid only	5(3%)
Steroid and CLL directed therapy only	3(1.8%)
Folic acid and CLL directed therapy only	27(16%)
Steroid, folic acid and CLL directed therapy	18(10.7%)
CLL directed therapy only	45(26%)

Among the 93 patients who took CLL directed therapy, the details of chemotherapy start date was available for 72 patients only. The time from diagnosis of CLL to start CLL directed therapy ranged between immediately after diagnosis (0 months) to a maximum of 72 months with a mean of 6.34 months (SD± 13.1). However the median time to start therapy was 1 month after the diagnosis which showed majority of patient who required CLL directed therapy did require therapy in their first few months of follow up.

The most common first line CLL directed treatment regimen used was Bendamustin-Rituximab(BR) which was used in 26(28%), followed by Chlorambucil in 24(25.8%), R-CVP (Rituximab, Cyclophosphamide, Vincristine, Prednisolone) in 19(20.4%) of patients and CVP in 10(10.8%) of patients. The number of cycles given range between 1 cycle and 9 cycles with a mean of 5.3(SD±1.9) and median of 6 cycles.

The commonest indication for first line CLL directed therapy was Rai stage 3 or 4 disease in 40(43%) of patients, followed by unclear or undocumented indication in 26(28%) of patients and bulky disease in 8(8.6%) of patients. The details of type and indication to start first line therapy are presented in Table 4 below.

Table 4: Types of first line CLL therapy and indications to treatment

Type of first line CLL directed therapy given		Indications for first line CLL directed therapy	
Therapy	**Number (%)**	**Indications**	**Number (%)**
BR	26(28%)	Rai Stage 3 or 4 disease	40(43%)
Chlorambucil	24(25.8%)	Unclear(Undocumented)	26(15.4%)
R-CVP	19(20.4%)	Bulky disease	8(8.6%)
CVP	10(10.8%)	Significant B symptoms	5(5.4%)
CR	7(7.5%)	Rai Stage III or IV + Bulky disease	5(5.4%)
CHOP	4(4.3%)	B symptoms+ Bulky disease	3(3.2%)
FCR	2(2.2%)	Stage III or IV disease+ B symptoms	2(2.2%)
		Lymphocyte Doubling Time(LDT)<6 months	2(2.2%)
FR	1(1.1%)	B symptoms+ LDT<6 months	1(1.1%)
		Autoimmune cytopenia refractory to steroid	1(1.1%)

During chemotherapy treatment interruptions were documented in 42(45.2%) of the patients. There was no treatment interruption in 33(35.5%) of patients and for 18(19.4%) information about treatment interruption was incomplete. Among the 42 patients in 23(54.8%) of them treatment was interrupted due to adverse effect of CLL therapy, whereas in 6 patients (14.3%) interruptions were due to financial constraint to pay for therapy, and in 2 (4.8%) patients the reason for interruption was unavailability of the therapy to buy and in 9(21.4%) interruption of therapy was due to patient defaulting to come for next therapy session but reasons for defaulting were not specified. For one patient treatment was discontinued as he did not have convincing indication to start therapy from the outset.

Among the 26 documented therapy related adverse effect requiring treatment interruptions, 22(84.6%) were severe cytopenia related (majority severe neutropenia), 1 (3.8%) was life threatening Rituximab related infusion reaction, 3 (1.8%) were infections not related to neutropenia during chemotherapy.

Looking at the response to first line therapy, among the 93 patients who received CLL directed therapy 58 patients had well documented response status. Among these, 22 (23.9%) had complete remission, 30(32.6%) had partial remission, and 6(6.5%) had no response. Another 18(19.6%) had some kind of response but information available was not complete enough to label them as either complete or partial response. A total of 14(15.1%) defaulted their first line therapy as a result response status could not be documented. 3(3.3%) of the patients are still on their first line chemotherapy during the write up of the findings.

When the relation of response to the type of therapy was looked into patient who took BR regimen had the highest rate of response compared to other regimens as high as 20(76.8%) of patients who took BR regimen had response. 14(53.6%) of the 26 patients who took BR as a first line therapy had complete remission whereas CR rates was 26.3% in patients who took R-CVP, 8.6% in Chlorambucil group and none in the CVP group. In terms of partial remission it was 23% in BR, 47.3% in R-CVP, 20% in CVP and 34.7% in the Chlorambucil group which were the four most frequently given first line regimen.

Among the total 70 patients who had response to first line therapy, 40(57.1%) relapsed. 18(25.7%) are on remission and still on follow up, however 12(17.1%) discontinued their follow up after responding to initial

CLL therapy and current remission status is unknown. Among the 40 patients who relapsed, relapse information was available for 36 of them. Time to relapse after completion of therapy ranged between 1-40 months with a median of 6.5 months. Majority 63.9% relapsed within the first year and 37.1% relapsed beyond 1 year of completing therapy.

However, among the relapsed patients only 25(62.5%) of them required second line of therapy. One additional patient who had refractory diseases after first line therapy also took second line therapy making the number of patient who required second round of CLL therapy 26. The commonest indication for second line CLL therapy was still Rai stage 3 and 4 disease followed by bulky disease. The most common regimen given as a second line of therapy was BR given for 13(52%) followed by R-CVP given for 3(12%). Other regimens used where CR, Chlorambucil and Bendamustine alone. For 3 patients treatment was planned but not given as patients could not afford for further therapy.

Regarding outcome after second line therapy, 11(47.8%) achieved complete remission, 4(17.4%) achieved partial remission, 6(26%) defaulted their second line therapy, 1 patient had no response and 1 patient is still on chemotherapy and too early to assess response status.

When Progression Free Survival (PFS) analysis was done using the Kaplan Meier method for all patients who took first line CLL therapy, the mean PFS was 21.8 months and the median PFS was 21 months.

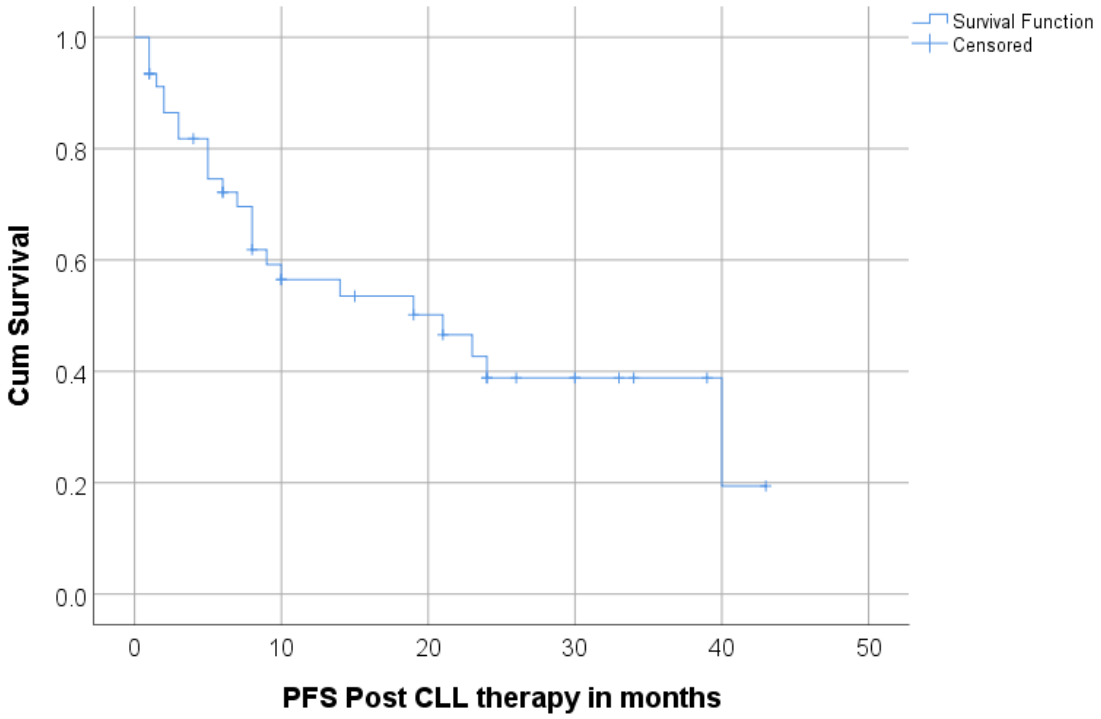

Figure 4: Progression Free Survival (PFS) post CLL therapy

Coming to the final information, of all the 169 CLL patients seen at TASH between from September 1, 2019 to August 31, 2022, 94 patients (55.6%) have discontinued their follow up at TASH, 30(17.8%) are

on follow up with maintained response following therapy, 27(16%) are on follow up with stable disease without requiring any CLL directed therapy so far and 18(10.7%) are on follow up with relapsed disease.

Further inquiry via phone call was made for the 94 patients who are lost from follow up clinic and 47 patients (50%) could not be reached with repeated calls. Their phone number was not working, permanently switched off or wrong number registered on I-care system. Among the 47 patient whom we were able to reach, 31(33%) of them are confirmed to have died making the proportion of confirmed death 18.3% from the whole cohort. Among this 22(23.4%) died at home, 6(6.4%) died at TASH, 3(3.2%) died at other hospital. 16 patients (17%) of the 94 who are lost from follow up clinic are confirmed to be alive and most are having follow up at a nearby hospital.

Regarding overall survival (OS) analysis the Kaplan Meier method was used to determine the mean and median overall survival for the whole cohort. Patients who were alive were censored on last data cutoff date of December 31, 2022 and the last date of follow up was used for those who discontinued follow up and last information is unknown. For patients who have died date of death was used for survival analysis. Accordingly, the mean overall survival for the group was 72.9 months with a median overall survival of 96 months.

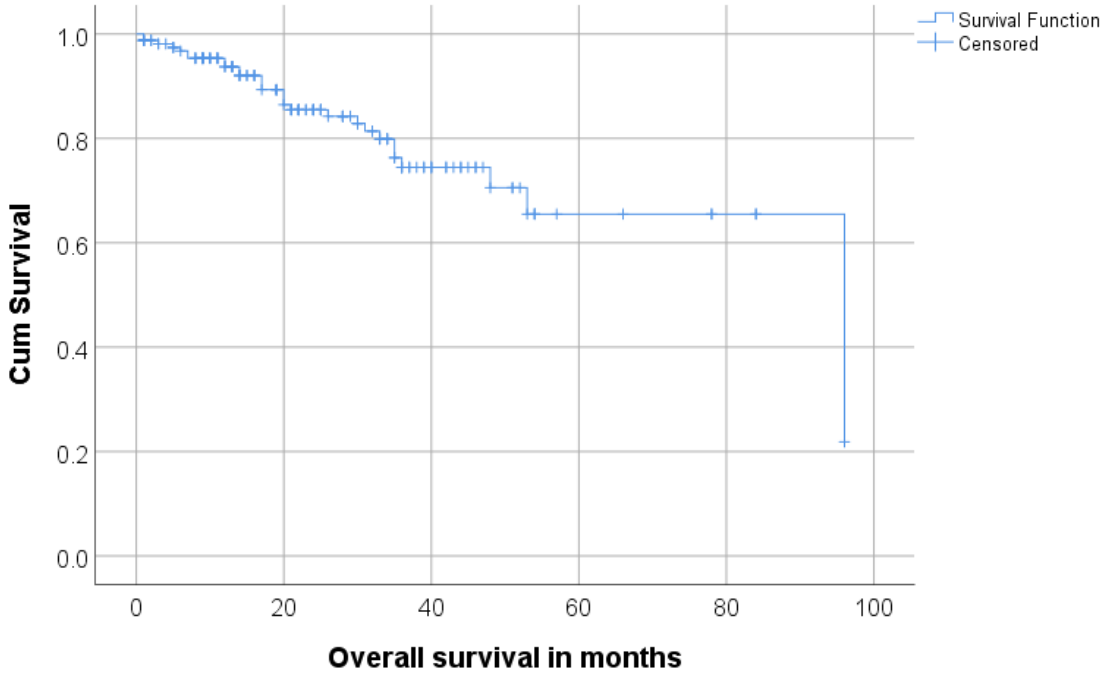

Figure 5: Overall Survival (OS) of CLL patients

7. Discussion

The mean age at diagnosis for CLL patients in our study was 57 years which is only slightly higher than in the study done at TASH about 30 years back by Shamebo et al which was 55.6 years.[4] However, it was slightly lower than the findings of recent studies from other African countries. A recent study from Sudan published in 2022 by Basabaeen et al reported 63 and 64 years for females and males respectively and a study from Senegal by Sall and colleagues reported the mean age at presentation to be 61 years where as a study from Kenya by Mulua-Babu et al reported 62.1 years.[8, 11, 12] The median age in our study was 58 years which was lower than the finding of a study from India by Agrawal et al which reported a median age of 61 years.[13] Nevertheless , all these findings from developing countries show that patients are diagnosed about a decade earlier than developed countries where the mean and median age at diagnosis are 70 years and above.[14,15]

As expected CLL is diagnosed more often in male patients than female patients with M: F ratio of 1.91:1 in our study which was close to the findings from western set ups.[14, 16] However this proportion is quite lower than the report by Shamebo et al which showed a M: F ratio of 3.6:1, the finding from Sudan and Senegal which reported a M: F ratio of 2.55:1 and 3.44:1. [4,8,11] The reason why females are relatively being diagnosed with CLL more often than previous studies in Ethiopia should be looked into. This could be due to a true increase in the incidence of CLL in females, an improvement in health seeking behavior of female patients or even erroneous diagnosis of other lymphoproliferative neoplasms which are thought to be more common in females such us Follicular lymphoma as CLL, as in our study diagnosis was mostly based on morphology alone.

According to our findings, the most common presenting symptoms were swelling on the cervical area or other lymph node sites and constitutional symptoms and the most common physical finding was lymphadenopathy. Most other studies also reported non-specific symptoms such as fatigue and constitutional symptoms as the top presenting symptoms and lymphadenopathy to be the commonest physical findings. [4, 8, 11, 13]

Unlike previous findings only 21.8% of the patients had advanced stage of diseases (Rai stage 3 or 4 disease) during initial presentation. Majority of the patients (71.3%) had non- advanced stage (Rai stage 0-2) at the time of diagnosis. This is contradicting to the finding by Shamebo et al some 30 years back at the same set up which reported advanced disease to contribute to 56% of the cases at initial presentation. [4] The proportion of advanced disease in our study which is only 21.8% is slightly closer to the 29.5% report from India but it is a way far lower than the findings from studies in Kenya, Sudan and Senegal which reported 38.8%, 49.1% and 62.5% respectively. [8, 11, 12, 13] The reason for such a low proportion of advanced disease might be as a result of early diagnosis and referral due to improved health access and knowledge in local health facilities in recent years. The fact that 11 patients were asymptomatic and diagnosed on routine evaluation is an indicator to this. In addition, a selection bias as only few admitted patients who are likely to have advanced disease were included in the study due to unavailability of charts from medical records room is also likely to contribute to a low number of advanced disease.

Some studies reported that advanced stage of disease at presentation is more common in males than females.[17] This was not true in our study. Even though on the contrary female patients had higher percentage

of advanced disease at presentation (34.6%) than males (25.7%), this difference was not statistically significant on Spearman rho test with a P-value of 0.54.

18.3% of the patients in our study were diagnosed and treated for autoimmune cytopenias associated with CLL. This number is higher than the 11.9% and 5.6% reported by Egyptian and Indian studies. The Egyptian study reported AIHA to be the commonest form of autoimmune cytopenia associated with CLL similar to our finding. [18, 19]

In terms of mode of diagnosis, in our study 79.3% of the diagnosis was made only based on morphological evidences. Only 19.5% of the patients had immunophenotypic confirmation of their diagnosis. This was only better than the study from TASH by Shamebo et al published 30 years back and the study from Nigeria which was published in 2010, in which diagnosis was only based on morphology. [4, 20] However, most recent studies even from developing countries like Sudan, Senegal and Kenya immunophenotyping was conducted in all CLL patients to ascertain diagnosis and it was rather put as one of the inclusion criteria. [8,11,12,21] This shows that poor utilization of immunophenotyping in the diagnosis of CLL is a major limitation in our set up that needs urgent solution.

In our study a total of 93 patients (55%) took CLL directed therapy at one point during their follow up and the rest 76(45%) did not require CLL directed therapy apart from supportive treatment like folic acid and steroid. Similarly a study from India reported 41.3% of their cohort remained on observation where as 56.3% of the patients required chemoimmunotherapy.[19] In our set up the commonest regimen used was BR which was used in 26(28%), followed by Chlorambucil in 24(25.8%) where as in the Indian study the commonest regimen was Chlorambucil±steroid used in 52.2% followed by BR regimen which was used in 31.6%. A 2019 study from Nigeria also reported Chlorambucil+ Prednisolone to be the commonest regimen used in 43.1% of patients. However, a real world data from Turkey published in 2020 showed that Fludarabine based chemoimmunotherpy regimen is the commonly used first line regimen accounting for 50% followed by Bendamustine based regimen used in 15% of patients. [19, 22, 23] As generally expected patients with advanced disease are likely to be started on therapy earlier than those with non-advanced disease. Accordingly, in our study the ANOVA test showed that a significant inverse correlation of Rai stage at the time of diagnosis with the time to start CLL directed therapy with a P value of 0.032.

Similar to our finding BR had the highest complete remission of 77.2% in the Indian study even higher than our finding which was 53.6% compared with other regimens used. In order to look into this possible association cross tabulations and Chi-square test were performed which showed a statistically significant association of type of regimen used with treatment response with a P-value of 0.002 on likely hood ratio. Despite having excellent response rate BR regimen was associated with a higher rate of Grade 3-4 neutropenia according to the Indian study. [19] Similarly in our study BR regimen was the commonest regimen associated with highest rates of therapy related complication with a P value of 0.001 on Chi square test.

Looking at other factors affecting treatment response, there was a notable significant correlation between sex of patients and response to first line therapy with females having better CR rates than males. The CR rates in females was 41.1% versus only 13.8% in males which was statistically significant on Chi square test with P- value of 0.003. This finding was consistent with the finding of Catovsky et al which demonstrated that females respond better to CLL therapy than males. [17] Similarly, response to therapy was

also affected by age. Those below the age of 50 years have higher rates of CR rates than those above the age of 50 with significant P-value of 0.005 using the spearman rho method of correlation test.

The relapse rate among responders was 57.1% in our study which is higher than the finding of the Indian study which reported a lower relapse rate of 35.5%. [19]

Factors influencing relapse were looked into and among these the significant factor affecting relapse was type of first line regimen which showed significant association with a P-value of 0.011 on likelihood ratio of Chi-square test. Patients who took BR are likely to stay longer in remission than others. Male sex was also associated with a higher risk of relapse. In our study while 71.4% of males relapsed only 35.7% of females had relapse with a statistically notable difference with a P-value of 0.01 on Chi square test. This finding might be in coherence with the finding of Catovsky that female sex was independently associated with better response to CLL therapy and better survival.

Multinomial regression analysis was done to see if the binary associations are persisting despite potential confounders. Among the factors which are significantly affecting treatment response to first line therapy are the age and sex of the patient, the type of chemotherapy used and treatment interruption. Among the factors affecting relapse rate, only sex of the patient and presence of treatment interruption had significant P- values. Details are summarized on Table 5 below.

Table 5: Factors affecting treatment response and risk of relapse

Treatment response		**Risk of relapse**	
Factors	**P- value**	**Factors**	**P-value**
Age	0.005	Age	0.094
Sex	0.027	Sex	0.024
Rai Stage at diagnosis	0.408	Rai Stage at diagnosis	0.791
Chemotherapy regimen	0.027	Chemotherapy regimen	0.997

The commonest second line regimen used after relapse was BR both in our study and the study from India. [19] The proportion of patients who are lost from follow up was 55.6% in our study which is much higher than the 17.1% reported by the Indian study. The reason behind this high rate of loss from regular follow up needs to be looked into through further focused research but financial constraints and logistic problems are likely to contribute to such high loss from regular follow ups.

With regards to survival association, Kaplan Meier curve with log rank test was used to see if PFS was associated with any factors and accordingly female patients had better PFS with median PFS not reached while male patients had median PFS of 8 months with significant P value of 0.006 on log rank test. However there was no statistically significant difference in terms of overall survival between male and female patients which was contrary to the finding by Catovsky et al.

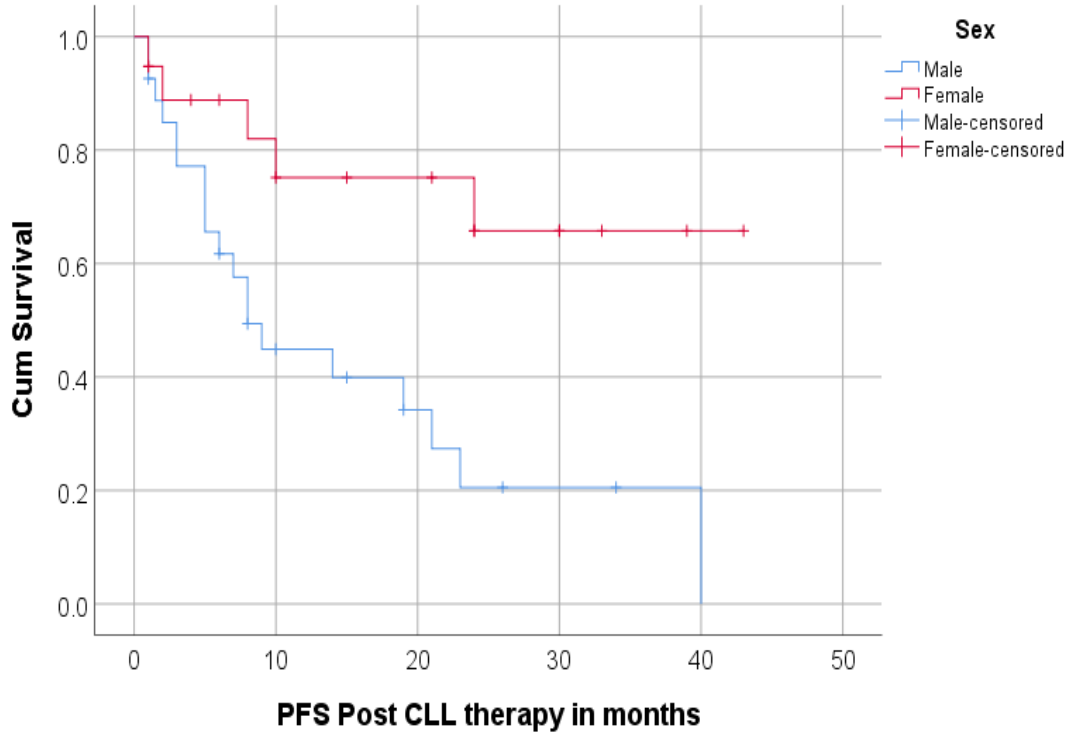

Figure 6: Effect of sex on Progression free survival (PFS) post CLL therapy

In terms of overall survival even though there was no statistically significant difference between male and female patients, there was statistically significant difference between those patients with age 50 and less and those above the age of 50 with the former having better overall survival. Those age above the age of 50 had a median OS of 96 months and in those younger than 50 the median overall survival was not reached with significant P-value of 0.001 on log rank test as depicted on Figure 7 below. This finding is comparable with the finding of Parikh et al which concluded younger CLL patients have better survival than older CLL patients. However according to another paper published in 2016 by Pulte et al even though in general, survival decreased with age, the age-related disparity was small for patients younger than 75.

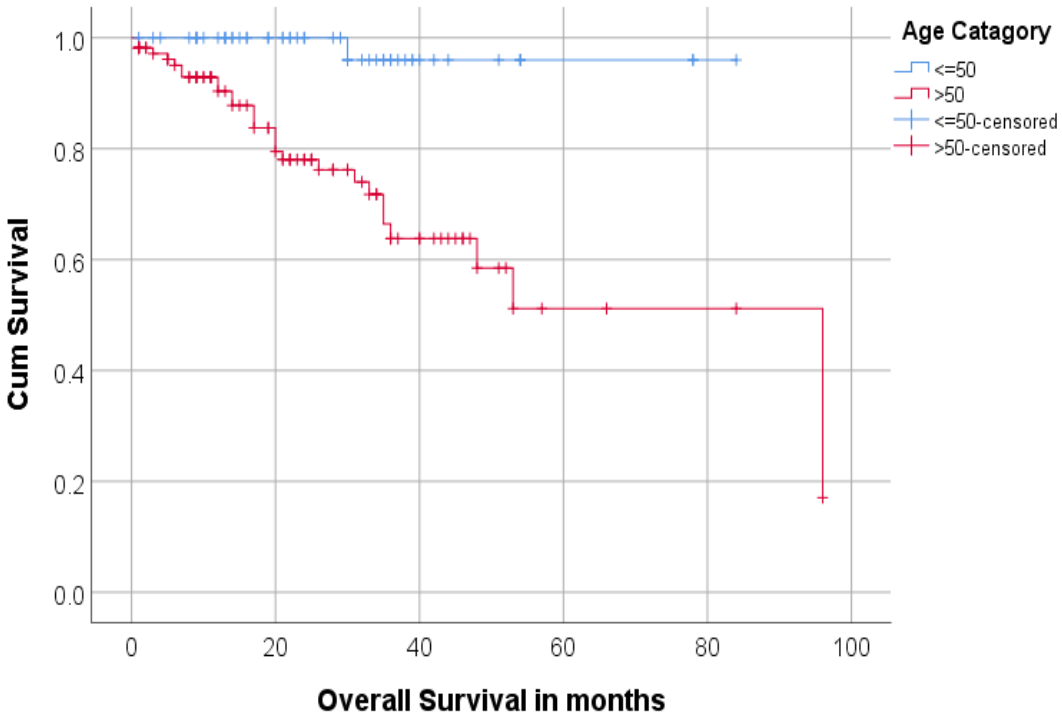

Figure 7: Effect of age on Overall Survival (OS) in CLL patients

8. Conclusion

Chronic Lymphocytic Leukemia is a common hematologic malignancy seen at Tikur Anbesa Hospital. The clinical presentation of patients with CLL in our set up is similar with most centers in Africa and worldwide relatively with slightly younger mean age of presentation with male dominance. The proportion of advanced disease seems to have lowered compared from previous findings. Diagnosis of CLL is mainly based on morphology and there is a critical limitation of accessing immunophenotyping. Response to therapy are comparable with other similar set ups. Age, sex and type of regimen affect the type of response, sex is the major factor affecting risk of relapse and progression while age is the major factor affecting overall survival. The lost to follow up and death at home rate is very high and causes leading to this should be looked into.

9. Recommendation

Chronic Lymphocytic Leukemia is one of the commonest hematologic diseases seen worldwide. CLL belongs to a wider class of hematologic neoplasm called lymphoproliferative disease, however with its own distinctive clinical picture, genetic signature as well as outcome to treatment. Therefore, making distinct diagnosis of it is vital in prognostication as well as treatment of patients. As it is a chronic form of hematologic malignancy it requires close follow up of patients and graded therapy depending on the need at a particular time.

According to our finding, a very important diagnostic modality of immunophenotyping is lacking from our center which poses a major limitation of ascertaining the diagnosis of CLL among the different types of lymphoproliferative neoplasms. In addition to that, investigative modalities of prognostication such as cytogenetic tests which have paramount importance on deciding the type of therapy are lacking. Hence, we recommend concerned bodies such as the FMoH, Tikur Anbesa Hospital, NGOs and health professionals to work together on acquiring such investigational modalities at least at one center in the country which will have a major impact in improving the care of CLL patients.

In terms of therapy, newer modalities of targeted therapy such BTK inhibitors and BCL2 inhibitors are not available which are vital in the primary treatment of high risk patients and treatment in relapse setting. We believe that the currently existing immunotherapy such as Rituximab should be made available in a sustainable manner but also action towards acquiring the newer targeted therapies should be taken by concerned bodies in order to improve the survival of CLL patients.

The other major problem observed in our finding is a very high loss from follow up. Therefore, we recommend further studies focusing on identification of the reason for such a high loss and implementation of a better patient retention strategy addressing the specific issues identified.

10. Strength and Limitations

The strength of this study is it is one of the very few studies in Ethiopia which tried to study Chronic Lymphocytic Leukemia which is the commonest type of leukemia worldwide. Especially recent changes in clinical presentation and treatment outcome after the advent of combination chemoimmunotherapy was lacking as the only study focusing on CLL was conducted some 30 years back at TASH. It has also included relatively larger number of patients and it tried to gather detailed information regarding all aspects of the disease including both clinical profile as well as treatment outcome.

Even though it was not the main objective, it also tried to assess major limitation in diagnostic modalities, treatment availability and limitations in patient retention that are existing in the set up.

However, the major limitation of our study is the retrospective nature of the study which was quite hampered by poor documentation, and missing or incomplete data. This might have affected the depth and quality of the study. In addition to that, as the lost to follow up rates from follow up hematology clinics were very high, which might affect the quality of the result. The other limitation is probably the difficulty to enroll all cases of CLL as there was difficulty of accessing the hard copy of medical record chart of significant number of in-patients due to a poor storage and retrieval system at the hospital which might have led to some selection bias.

11. Reference

1. *Key Statistics for Chronic Lymphocytic Leukemia, American cancer society Last Revised: January 12, 2021*
2. *Ronald Hoffman et al. - Hematology_ Basic Principles and Practice-Elsevier (2017)., Chapter 77, page 1244*
3. *Karakosta M., Delicha EM, Kouraklis G & Manola KN. Association of various risk factors with chronic lymphocytic leukemia and its cytogenetic characteristics. Arch Environ Occup Health; 2016 Nov;71(6):317-329*
4. *Shamebo M , Gebremedhin A. Chronic lymphocytic leukemia in Ethiopians. East Afr Med J 1996 Oct;73(10):643-6.*
5. *Yiyi Yao Y, Lin X, Li F, Jin J et al. The global burden and attributable risk factors of chronic lymphocytic leukemia in 204 countries and territories from 1990 to 2019: analysis based on the global burden of disease study 2019. BioMedical Engineering OnLine volume 21, Article number: 4 (2022)*
6. *Bewarder M, Stilgenbauer S, Thurner L ,& Kaddu-Mulindwa D. Current Treatment Options in CLL. Cancers (Basel). 2021 May; 13(10): 2468.*
7. *Deepesh P Lad,, V Tejaswi, Pankaj Malhotra et al. Establishment of a comprehensive chronic lymphocytic leukemia clinic at a tertiary referral center in India. Blood Adv 2018 Nov 30;2(Suppl 1)*
8. *Abibatou Sall, Awa Oumar Touré, Fatimata Bintou Sal et al. Characteristics of chronic lymphocytic leukemia in Senegal. 2016; BMC Hematology volume 16, Article number: 10*
9. *Tefferi A & Killmann N M-B. Globalization of treatment strategies in leukemia: challenges and responsibilities Leukemia volume 22, pages1093–1094 (2008)*
10. *Molica S. The evolving role of time-limited targeted therapy in chronic lymphocytic leukemia. Expert Review of Anticancer Therapy; 05 Oct 2020, Volume 20- Issue 12. Pages 1015-1019*
11. *Basabaeen A.A., Abdelgader E.A., Babekir E.A., Abdelateif N.M., Abdelrahim S.O., Ali O., et al. Characteristics of Chronic Lymphocytic Leukemia in Sudanese Patients. Asian Pac J Cancer Care 2022, 3 (7), 467-474*
12. *Mulwa-Babu E., Paresh D.,·Riya M. Chronic lymphocytic leukemia in Kenya: an immunophenotypic and clinicopathologic study. J. Afr. Cancer (2013) 5:192-197*
13. *Agrawal N, Naithani R, Mahapatra M, Panigrahi I, KumarR, Pati H.P.,Saxena R & Choudhary V.P. Chronic lymphocytic leukemia in India A clinico-hematological profile, Hematology 2007, 12:3, 229-233*
14. *Hallek M. Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. Am J Hematol. 2015 May;90(5):446-60. doi: 10.1002/ajh.23979. PMID: 25908509.*
15. *Pfeil AM, Imfeld P, Pettengell R, Jick SS, Szucs TD, Meier CR, Schwenkglenks M. Trends in incidence and medical resource utilisation in patients with chronic lymphocytic leukaemia: insights from the UK Clinical Practice Research Datalink (CPRD). Ann Hematol. 2015 Mar;94(3):421-9. doi: 10.1007/s00277-014-2217-7. Epub 2014 Sep 16. PMID: 25219890.*
16. *Yang O, Yichen L, Lili J et al. Trends in Disease Burden of Chronic Lymphocytic Leukemia at the Global, Regional, and National Levels From 1990 to 2019, and Projections Until 2030: A Population-Based Epidemiologic Study. Frontiers in Oncology J. 2022 Volume 12*

17. *Catovsky D, Wade R, Else M. The clinical significance of patients' sex in chronic lymphocytic leukemia. Haematologica. 2014 Jun;99(6):1088-94. doi: 10.3324/haematol.2013.101378. Epub 2014 Mar 21. PMID: 24658818; PMCID: PMC4040913.*
18. *Atef B., Azmy E., Aladle D., Mabed M. The prevalence and prognostic significance of autoimmune cytopenias in a cohort of Egyptian patients with chronic lymphocytic leukemia. Hematology/Oncology and Stem Cell Therapy Volume 12, Issue 2, June 2019, Pages 97-104*
19. *V. Tejaswi, ; Deepesh P. Lad, ; Nishant Jindal et al. Chronic Lymphocytic Leukemia: Real-World Data From India. JCO Global Oncol 6:866-872. 2020 by ASCO*
20. *Salawu L, Bolarinwa RA, Durosinmi MA Chronic lymphocytic leukaemia: a-twenty-years experience and problems in Ile-Ife, South-Western Nigeria. African Health Sciences 2010; 10(2): 187 - 192*
21. *Elglee R.A., Ahmed M. Osman I.M. Clinical and Haematological Pattern of Chronic Lymphocytic Leukaemia in Sudanese Patients. International Blood Research & Reviews 7(1): 1-10, 2017; Article no.IBRR.31359 ISSN: 2321–721*
22. *Madu AJ, Korubo K, Okoye A et al. Presenting features and treatment outcomes of chronic lymphocytic leukemia in a resource poor Southern Nigeria. Malawi Med J. 2019 Jun; 31(2): 144–149*
23. *Demirkan F, Sevindik O.G. CLL-395: Real-World Data from the Turkish National Chronic Lymphocytic Leukemia Registry. Clinical Lymphoma, Myeloma and Leukemia. Volume 20, Supplement 1, S229, September 2020*
24. *Parikh SA, Rabe KG, Kay NE, Call TG, Ding W, Schwager SM, Bowen DA, Conte M, Jelinek DF, Slager SL, Shanafelt TD. Chronic lymphocytic leukemia in young (≤ 55 years) patients: a comprehensive analysis of prognostic factors and outcomes. Haematologica. 2014 Jan;99(1):140-7. doi: 10.3324/haematol.2013.086066. Epub 2013 Aug 2. PMID: 23911703; PMCID: PMC4007929.*
25. *Pulte, D., Castro, F.A., Jansen, L. et al. Trends in survival of chronic lymphocytic leukemia patients in Germany and the USA in the first decade of the twenty-first century. J Hematol Oncol* ***9****, 28 (2016). https://doi.org/10.1186/s13045-016-0257-2*

Data collection questionnaire for the retrospective study of patients with Chronic Lymphocytic Leukemia (CLL) at the TASH

Serial No: _____ Chart Number (MRN): _____

Phone number: _____

A. Demographic data:

Initial: _____ Region: _____

Age: _____ Sex: _____

Date of CLL diagnosis (BM/ flowcytometry report date): _____

Date of Admission (If patient was ever admitted): _____

B. Presenting symptoms:

B1Presence of infection during presentation: 1. Yes 2. No 3. Unknown

B2. Anemia symptoms: 1. Yes 2. No 3. Unknown

B3. Bleeding tendencies: 1. Yes 2. No 3. Unknown

B4. Constitutional symptoms 1. Yes 2. No 3. Unknown

B5. Neck or swelling at another site 1. Yes 2. No 3. Unknown

B6. Abdominal Swelling 1. Yes 2. No 3. Unknown

B7 Asymptomatic (incidental diagnosis) 1. Yes 2. No

C. Duration of illness (in weeks): _____

D. Presenting signs:

D1. Fever $\geq 38^0$C: 1. Yes 2. No 3. Unknown

D2. Pallor: 1. Yes 2. No 3. Unknown

D3. Mucocutaneous bleeding: 1. Yes 2. No 3. Unknown

D4. Lymphadenopathy: 1. Yes 2. No 3. Unknown

D5. Raised JVP/S3 gallop/ Peripheral edema: 1. Yes 2. No 3. Unknown

D6. Splenomegaly: 1. Yes 2. No 3. Unknown

D7. If yes for splenomegaly, size in CM BLCM:_____

D8. Hepatomegaly: 1. Yes 2. No 3. Unknown

D9. If yes for hepatomegaly, Size in CM BRCM: _____

D9. Other, specify: _____

E. Laboratory findings at presentation:

E1. WBC (/μL):_____E2. Hb (g/dL): _____E3. Platelet count(/μL):_____

E4. Total lymphocyte count (%) _____E5. BM lymphocyte percentage (%) _____

E6. LDH(IU): _____ E7. Uric Acid(mg/dL): _____E8. Creatinine (mg/dL):_____

E9. Tumor lysis syndrome (according to Cairo Bishop Criteria) 1. Yes 2. No 3. Unknown

E10. Total Bilirubin_____ E11. Direct Bil _____

E12. Reticulocyte count _____

E13. DAT (Coomb's Test) A. Positive B. Negative C. Not done

F. What is the Rai stage of the patient?

1. 0 2.I 3.II 4.III 5.IV

G. What is the Binet stage of the patient?

1. A 2. B 3.C

H. Which modality was used for diagnosis?

1. Morphology alone
2. Morphology with Immunophenotyping by flow cytometry
3. Morphology and Cytogenetic Analysis
4. Morphology, Immunophenotyping and Cytogenetic Analysis

I. If Immunophenotyping by flow cytometry, please record the findings.

_____

J. If cytogenetics done, the result is: _____

K. Comorbid condition at presentation?

K1. HIV 1. Yes 2. No 3. Unknown
K2. Hepatitis B 1. Yes 2. No 3. Unknown
K3. Hepatitis C 1. Yes 2. No 3. Unknown
K4. Cardiac disease 1. Yes 2. No 3. Unknown
K5. Diabetes Mellitus 1. Yes 2. No 3. Unknown
K6. Hypertension 1. Yes 2. No 3. Unknown
K7. Other, specify: _____

L. Did the patient develop any diagnosed autoimmune complication of CLL during his follow up?

1. Yes 2. No

M. Which autoimmune complications did the patient develop?

1. AIHA 2. ITP 3. Both

N. Status of treatment (Multiple choices possible)

1. Did not start any therapy
2. Took steroids
3. Took Folate
4. Took CLL specific therapy

O. If therapy was initiated what was the indication to start therapy? (Multiple choices possible)

1. Stage III or IV disease
2. Clinically significant B symptoms
3. Bulky disease/ Compressive symptoms
4. Autoimmune cytopenia not responding to steroids
5. LDT <6 months
6. Patients request (Cosmetic)
7. Unknown

P. If the patient has taken chemotherapy, what regimen did he took as a first line?

1. Chlorambucil
2. CVP
3. R-CVP
4. FCR
5. BR
6. Other (Specify)_____

Q. Chemotherapy start date in GC_____ R. Number of cycles given_____

S. Was there any treatment interruption?

1. Yes 2. No 3. Unknown

T. Why was treatment interrupted?

1. Due to side effects
2. Due to drug unavailability
3. Drug available but patient could not afford

U. Was there any complication noted during chemotherapy?

1. Yes 2. No 4. Unknown

V. What complications were noted during induction (multiple answers possible)?

1. Neutropenia /Neutropenic fever
2. TLS
3. Infusion reaction (Rituximab associated)
4. Hemolysis (Fludarabine associated)
5. Renal failure
6. Liver Injury
7. Other, specify _____

W. What was the outcome of the initial CLL directed therapy?

1. Achieved Complete Remission
2. Achieved Partial Response
3. Achieved No response
4. Defaulted
5. Died before treatment
6. Unknown

X. Did the patient relapse after initial therapy?

1. Yes 2. No 3. Unknown/Discontinued follow up

Y. If yes to the above question, when did he relapse after completion of the first therapy?

1. Within 3 months
2. 3-6 months
3. 6months to 1 year
4. 1 year- 2 years
5. Beyond 2 years

Z. Did the patient require therapy after relapse?

1. Yes 2. No

I. What was the indication for treatment this time?

1. Stage III or IV disease
2. Clinically significant B symptoms
3. Bulky disease/ Compressive symptoms
4. Autoimmune cytopenia not responding to steroids
5. LDT <6 months

6. Patients request (Cosmetic)
7. Unknown

II. What therapy was given after relapse?

1. Chlorambucil
2. CVP
3. R-CVP
4. FCR
5. BR
6. Other (Specify)_____

III. Chemotherapy start date in GC_____ IV. Number of cycles given_____

V. What was the outcome of the second CLL directed therapy?

1. Achieved Complete Remission
2. Achieved Partial Response
3. Achieved No response
4. Defaulted
5. Died during chemotherapy
6. Unknown

VI. How many subsequent relapses did the patient have? _____

VII. If the patient is currently alive,

IX1. Duration of outcome measures (in months) _____

IX2. What is his/her final condition/ final information about the patient?

1. Alive with stable disease
2. Alive with relapsed disease
3. Alive with refractory disease
4. Lost to follow-up during OPD appointments_____
5. Other, specify: _____

VIII. What is the current condition of the patient after he/she is lost to her follow up?(To be requested on phone call)

1. Died at home
2. Died at TASH
3. Died at other hospital
4. Alive (on follow up elsewhere)
5. Not responding to phone call

IX. If the patient died, when did he/ she died?_____

X. What was the presumed cause of death?(To be filled from chart if patient died at TASH or filled if the family known the exact cause)

1. Non- Neutropenic sepsis
2. Neutropenic sepsis
3. Tumor Lysis Syndrome
4. Disease progression
5. Hemorrhage into vital organ
6. Thrombo-embolism
7. Secondary Malignancy
8. Died of CLL unrelated causes
9. Summary of death unknown (Insufficient information)

Annex 2

Rai Staging System

The Rai staging system classifies CLL into three separate risk groups.

Stage	Characteristics
Low Risk (Stage 0)	• Abnormal increase in the number of lymphocytes in the blood and marrow
Intermediate Risk (Stages 1 & 2)	• Abnormal increase in the number of lymphocytes in the circulating blood and the marrow • Enlarged lymph nodes OR • Abnormal increase in the number of lymphocytes in the circulating blood and the marrow • Enlarged spleen and/or liver
High Risk (Stages 3 & 4)	• Abnormal increase in the number of lymphocytes in the circulating blood and the marrow • Anemia (hemoglobin <11g/dL) OR • Abnormal increase in the number of lymphocytes in the circulating blood and the marrow • Thrombocytopenia (platelet counts <100,000/uL)

Annex 3
Binet Staging System

The Binet staging system classifies CLL into three stages.

Stage	**Characteristics**
A Stage	• No anemia (hemoglobin ≥10g/dL) • No thrombocytopenia (platelets ≥100,000/mm^3) • Less than 3 areas of lymphoid tissue enlargement
B Stage	• No anemia (hemoglobin ≥10g/dL) • No thrombocytopenia (platelets ≥100,000/mm^3) • 3 or more areas of lymphoid tissue enlargement
C Stage	• Anemia (hemoglobin <10g/dL) • Thrombocytopenia (platelets <100,000/mm^3) • Any number of areas of lymphoid tissue enlargement