ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
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SURVIVAL STATUS AND PREDICTORS OF MORTALITY AMONG ACUTE LEUKEMIA PATIENTS ATTENDING ADULT HEMATOLOGY ONCOLOGY WARD AT TIKUR ANBESSA SPECIALIZED HOSPITAL ADDIS ABABA, ETHIOPIA.2019.

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A THESIS SUBMITTED TO SCHOOL OF NURSING AND MIDWIFERY, COLLEGE OF HEALTH SCIENCES, ADDIS ABABA UNIVERSITY PRESENTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN CLINICAL ONCOLOGY NURSING

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LIST OF ACRONYMS AND ABBEREVIATIONS

AAU	Addis Ababa University
ALL	Acute Lymphoblastic Leukemia
AL	Acute Leukemia
AML	Acute Myeloid Leukemia
CI	Confidence Interval
CLL	Chronic Lymphoblastic Leukemia
CML	Chronic Myeloid Leukemia
CR	Complete Remission
DFS	Disease Free Survival
ETB	Ethiopian Birr
FMOH	For Ministry Of Health
GC	Gregorian Calendar
HR	Hazard Ratios
HMIS	Health Management Information System
IARC	International Agency for Research on Cancer
INCTR	International Network for Cancer Treatment Report
MRN	Medical Record Number
PI	Principal Investigator
RSRs	Relative Survival Ratios
REC	Research and Ethics Committee
SEER	Surveillance, Epidemiologic and End Result
SES	Socio Economic Status
TASH	Tikur Anbessa Specialized Hospital
OS	Overall Survival
WBC	White Blood Cell

ABSTRACT

Background: Leukemia ranked tenth for cancer incidence and ninth for cancer deaths in the world. More than 78% of leukemia occurred in developing country and only 22% in developed countries. However, there is limited information that shows survival status and factors associated with death of adult acute leukemia patients in Ethiopia.

Objectives: the aim of this study was to determine survival status and determinant factors of acute Leukemia at Tikur Anbessa specialized hospital March to April 2019.

Methods: A five year retrospective cohort study was conducted involving all patients seen from January 2014 to December 2018. Patient's charts were reviewed between Marchs to April 2019. The data was analyzed using SPSS version 25.0. Kaplan–Meier Log-rank model was used to estimate the survival time of acute leukemia patients based on explanatory variables. Bivariate and multivariate Cox proportional hazards regression models was performed to identify the independent factors for mortality.

Result: Overall survival probability of acute leukemia was 0.21 and the median survival was 35 months with median follow-up of 17 months. Acute leukemia subtypes (HR: 4.9, 95% CI: 2.3-10.4,P value <0.00),history of relapse (HR: 3.9, 95% CI: 1.0-7.9, P< 0.002), age (HR:1.25,95% CI: 1-1.75,p<0.01),Hepatomegaly(HR:2.7, 95% CI: 1.36-5.36 , p<0.004) and splenomegaly (HR:2.29 95% CI: 11.2-4.4 ,p<0.014were determinant factors of the acute leukemia mortality.

Conclusion: Survival rate of acute leukemia patients in this study was very low as compared to other studies conducted in the developing as well as developed world. Advanced age, history of relapse, hepatomegaly, splenomegaly and leukemia subtype are determinant factors for acute leukemia. Strengthening cancer care centers, improving community awareness, timely diagnosis and treatment may be necessary to increase patient survival.

Keywords: Acute Leukemia, Associated Factors, Survival Status; Tikur Anbessa

CHAPTER 1: INTRODUCTION

1.1 Background

According to WHO report the incidence of cancer is increasing and estimates that 2040, the global burden is expected to grow to 27.5 million new cancer cases and 16.3 million cancer deaths(1). Cancer made second leading cause of death in the United States, following heart disease(2). People with lower socio economic status(SES) have greater exposure to cancer risk factors, like smoking and excess body weight, and barriers to effective cancer prevention, early detection, and treatment in addition to this number of genetic, life-style, therapeutic and environmental factors have been linked to an increased risk of leukemia(3).

American cancer society estimates that, 1,762,450 new cancer cases and 606,880 cancer deaths are projected to occur in the United States among this 150,980 new hematologic malignancies can expected from this around 60,300 new Leukemia cases 24,370 deaths from leukemia expected (14,270 males and 10,100 females) per year in USA(4). In Canada, leukemia is diagnosed at a rate of 15 cases per 100,000 persons, and accounts for 3% of all new primary cancers. Surveillance, Epidemiologic and End Result (SEER) database classified into leukemia one of four main types: acute lymphocytic (ALL), chronic lymphocytic (CLL), acute myeloid (AML), and chronic myeloid (CML). Acute leukemia (AL) is a diverse group of clonal hematopoietic disorders that are broadly categorized into two types: acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are depending upon the type of white blood cell that makes up the leukemia cells(5).

The World Health Organization (WHO) classifies ALL as either B lymphoblastic leukemia or T lymphoblastic leukemia. Historically, T-cell ALL patients have had a worse prognosis than other ALL, the relapse rate of T-cell ALL is greater than B-cell ALL cases, and T-cell ALL cases have shown less EFS than B-ALL cases(6). ALL subtypes more common in children and young adults (53% of new cases occur in persons < 20 years) and AML was mostly affects adults (accounts for 80% of acute leukemia in adults)(7). Leukemia's are a group of heterogeneous neoplastic disorders of white blood cells whose etiology is still obscure

although the role of ionizing radiation and benzene in the development of leukemia is well known(8).

According to a study by the University of Maryland Medical Center study, acute lymphocytic leukemia strikes about 6000 people in the entire United States of America, 300 in Australia and in the United Kingdom, the number is 8600 every year(9) and acute Myeloid Leukemia (AML) is one of the most common types of adult leukemia, with at least 13,000 individuals diagnosed each year in the U.S and incidence of AML increases with age, with 16.0 per 100,000 individuals age ≥ 65 years compared to 1.7 per 100,000 individuals age <65(10).

Acute leukemia does not usually form tumors. It generally is widespread throughout the bone marrow and, in some cases, has spread to other organs, such as the liver and spleen. Therefore, acute leukemia is not staged like most other cancers(11). Leukemia is an important cause of morbidity and mortality in Nigeria and increased incidence of leukemia among the youths (21-40years) whereas that of the older patients (61-70years) has decreased. AML, ALL takes 23.9% and 19.5% of all leukemia respectively (12).

1.2 Statement of the problem

According to International Agency for Research on Cancer (IARC) 2018 report cancer is the second leading cause of death globally and is estimated to account for 9.6 million deaths. Globally, about 1 in 6 deaths is due to cancer. Approximately 70% of deaths from cancer occur in low- and middle-income countries. Nearly every family in the world is touched by cancer, which is now responsible for almost one in six deaths globally(13). Leukemia is common hematologic disorders in Africa even though rarely diagnosed. There is a decline in mortality and higher probability of survival in the Western world due to advanced treatment modalities, early presentation by patients with availability of diagnostic tools. However, the same cannot be said for developing countries where the survival rate is very poor due to a number of strong limiting factors(12). According to cancer statics 2018 there was more than 24,370 deaths from leukemia deaths in USA(2).

According to International journal of cancer report cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. The burden of cancer is increasing in economically developing countries(2). Neoplasm is one of the first admission diagnosis followed by, diseases of the circulatory in Tikur anbessa hospital and also this study showed that most of the patients are coming to the department in locally advanced or metastatic stage. Hematologic malignancies are one of the fourteen top cancers in Ethiopia(14). Hematological malignancies are becoming major causes of morbidity and mortality in all age groups and leukemia have been shown to be a major health problem over the years with an increasing incidence(15).

More than seventy eight present of leukemia death occurred in developing and only 22% in developed countries and caused 9.3 million disability-adjusted life years in the world. Leukemia ranked tenth for cancer incidence and ninth for cancer deaths in the world among this AML is most prevalent form second to chronic lymphocytic leukemia as the most common subtype of leukemia in adults(16).

Leukemia is a common malignancy in children and adults that occurs approximately one in 70 persons develops leukemia in his or her lifetime(7). According to American blood cancer journal report acute leukemia is very aggressive in nature; urgent diagnosis and treatment have significant effect on survival(9). Incidence of leukemia and its burdens was very high for children's and young adults in Gondar northern Ethiopia in which leukemia was 1st leading hematologic malignancy(17).

1.3 Significance of the study

More than 78% of leukemia occur outside of high income countries, illustrating a clear demand for leukemia care in developing countries a mandatory issue(16). Cancer diagnosis was increasing from to time with varied outcomes, more than sixteen cancer diagnoses per 100,000 children ages 0 to 14 years and 72 cancer diagnoses per 100,000 adolescents and young adults ages 15 to 39 years in(18). Leukemia is a common cancer in worldwide and its survival status and associated factors of death were not mentioned more even though it was the common cancer in developing world(1). In Ethiopia where hematology oncology practice is so young, awareness' even among medical professionals about oncology is much inferior than expected even though prevalence of hematologic malignancy increases. In addition Ethiopia like most of sub-Saharan Africa countries shortage of cancer data shows survival status(19).

Although the prevalence of leukemia increasing and its burden was exceedingly high in Ethiopia, there is a still literature gap in study area which clearly shows the survival status and associated factors of acute leukemia death. Hence, this study is expected to provide area-specific information for decision-makers by visualizing leukemia survival status and its associated factors. At the same time it also fills the literature gaps in the country regarding survival status and associated Factors of acute leukemia.

CHAPTER 2: LITRETURE REVIEW

2.1 Survival status

Based on American cancer society latest report five year survival status of 90% for ALL subtypes and 66% for AML types(20). United States multiple registries based study shows five-year net survival approximately of the adult (15-99 years) US population varies with principal subtype (chronic lymphocytic leukemia, acute myeloid leukemia, and acute lymphocytic leukemia). Survival in subtypes 18.2% for acute myeloid leukemia and 44.0% for acute lymphocytic leukemia in USA (21) another American study showed that complete remission (CR) rate was 57% with 10% induction deaths, and estimated overall survival was 12% at 4 years(22). From Indian study overall survival at 6 years of analysis was 86%(23). Overall the 5-year relative survival rate for people diagnosed with leukemia between 2009 and 2013 in Korea shows that was 69.4%(24).

Consecutive study finding in Canadian intensive care leukemia patients shows that overall survival acute leukemia is 62% patients survived to ICU discharge, with almost similar survival in ALL and AML patients (64% and 62%, respectively)(25). Survival status from Nigeria study shows that it have a big variation in AML and ALL in which age-standardized 5-year net survival estimates that 52.0%. Five year survival for acute myeloid leukemia is 44 % and 77.7% for acute lymphocytic leukemia. For nearly all leukemia subtypes, survival declined age groups above 45 to 54 years. In this study there is survival variation between male and female and Men were found to have slightly lower survival than women(8).

Median survival of AML sub types 13.8 months and overall survival was 45.6 %. In this study increased age was greater risky for AML mortality in which age 50-70 was 2.2 hazards and age>70 was 3.2 hazards of death in relation with age less than 50 years, 3+7 (3 days of anthracycline and cytarabine 7 days of induction was positive predictor of mortality). presence of Monosomy and Trisomy have negative predictor (26). Remission rate in T-cell patients was 94% compared with 93% in B-cell patients. Similar to the results found in B-lineage patients, remission rates were higher in younger patients (98% at ages 15-29 is ,age between 30-49is93% and 79% in those 50 years of age and older)(27).Retrospective study

done in Britain shows that two year survival for ALL subtype leukemia is 85 % and one year survival is above 90 % (28).

According to ASCO finding the 5-year OS and EFS rates of the entire in study were 50.0% and 47.3% respectively, at an actuarial median follow-up time of 59 months. The 5-year OS and EFS rates of the stand risky cohort were 61% and 58.8% respectively, whereas OS and EFS rates of the high risky cohort were 27.2% and 23.6% respectively and induction mortality rate of 7.2% (29).Acute leukemia patients in critical patients five year disease-free survival approaches to 40% in younger patients and 15% in older adults and treatment-related mortality from remission induction therapy approaches 25%(30).

2.2 Factors associated with survival of leukemia

2.2.1 Socio demographic factors

Based on American study age, SES and health insurance are the main factors of leukemia poor survival (9)lack of insurance and other socio-economic factors may increase the risk of treatment delays or lead to early death(31). Acute leukemia, generally defined by age ≥60 years, has worse treatment outcomes than younger patients and has poor survival. This disparity may be due to biologic characteristics (32). Another US study show that leukemia subtype, sex, race are the determinant factors of survival in age female better survival than male patients and all leukemia subtypes, survival declined in successive age groups above 45 to 54 years(21).

Based on ASCO finding higher age at diagnosis (age > 20 but ≤ 40 years: HR, 1.6; and age > 40 years: HR, 2.2(29). Finding from Canadian study shows that age at the diagnosis for AML leukemia survival in which older ages are highly risky for death in comparison to younger age(5). Similarly age based study from UK national cancer intelligence network shows that those aged 14 or younger, more than more than 90% will survive their leukemia for 5 years or more after they are diagnosed, those aged between 15 and 24, almost 70% will survive their leukemia for 5 years or more after diagnosis, those aged between 25 and 64, almost 40% will survive their leukemia for 5 years or more after they are diagnosed, those aged 65 or older, almost 15 out of 100 (almost 15%) will survive their leukemia for 5 years or more after diagnosis(33).

2.2.2 Hematologic and clinical factors

Based on Wisconsin Hospitals and Clinics university report history of relapse and site of relapse are the major factors of leukemia survival in adult patients(34). Another article from journal of global oncology finding in developing country shows that median time for relapse is 14 month, isolated medullary and extra medullary, CNS and Combined medullary and extra medullary where the major site of relapse(29). Actuarial disease-free survival at 5 years was 21% for all patients, 43% for patients in first remission and 9% for patients in relapse. Factors significantly associated with improved survival and disease-free survival included younger age and being in first remission. Risk of relapse correlated only with disease status at transplantation: patients who underwent transplantation in relapse had a 9-fold increased risk compared with patients who underwent transplantation in first remission. Patients with Philadelphia chromosome-positive ALL had survival and relapse rates similar to patients with normal cytogenetic(35).

Follow up study from Japanese Journal of Clinical Oncology shows that age of older than 30 years ,erythrocytes, leukocytes, immophenotype were likely to be associated with shortened survival for ALL leukemia(36) another Canadian study indicates that there is association between age at admission and septic shock with leukemia survival(25). B-cell ALL was more prevalent in females and T-cell was common in males Central nervous system (CNS) disease was found to be more common in patients with T-cell compared with those with pre–B-cell disease (9.6% vs 4.4%) and CNS involvement was associated with poorer survival and outcome of relapsing patients was very poor and that patients with T-cell disease had a 5% 5-year survival compared with 8% in those with B-ALL(27).

Another finding shows that white blood cell (WBC) count of more than 100,000 at the time of diagnosis is linked with a less favourable prognosis similar to relapse history, number of relapse and site of relapse have strong relation with prognosis of leukemia. Specially spread to brain and spinal cord (called the central nervous system, or CNS) is strong prognostic factor for poor survival (37).

Poor prednisolone response on day 8 are 2.1 times hazard of death in comparison to good prednisolone response(29). From Nigeria study hemoglobin, total leucocyte count, poverty, illiteracy, ignorance, unavailability of drugs, high cost of therapy and often time's lack of supportive blood components and Platelet count are determinant factors of leukemia survival(8) and also failure to achieve CR may be attributed to death during chemotherapy-induced bone marrow hypoplasia or to drug resistance manifested either as failure to achieve hypoplasia or as persistent leukemia after recovery from hypoplasia which is a major predictor of mortality(38).

Study done Iran shows that hepatosplenomegaly have a significant effect on survival status of acute leukemia patients(39).According to American hematology society patients with splenomegaly are at a higher risk for engraftment failure or delayed engraftment leads to poor survival(40).Leukemia immunophenotype was prognostic, with patients who had T-cell ALL having a higher relative risk of death than those with B-cell. ALL high-risk stratified patients and WBC was the most significant predictor of survival, with higher WBC (WBC $\geq$ 50,000/μL) resulting in poorer outcome and high-risk stratified subgroups relative risk of death was 3.6-fold than standard risky(41).

2.3 Conceptual Framework

By considering the above review on s***urvival status and predictors of mortality among acute leukemia were*** summarized on the conceptual framework presented below. This shows how the particular variables in study connect with each other and identifies the variables required in the research investigation. This conceptual framework is developed by assuming ***survival status and predictors of mortality among acute leukemia patients*** was also be related to those factors as reviewed from different literature majorly from the referenced articles.

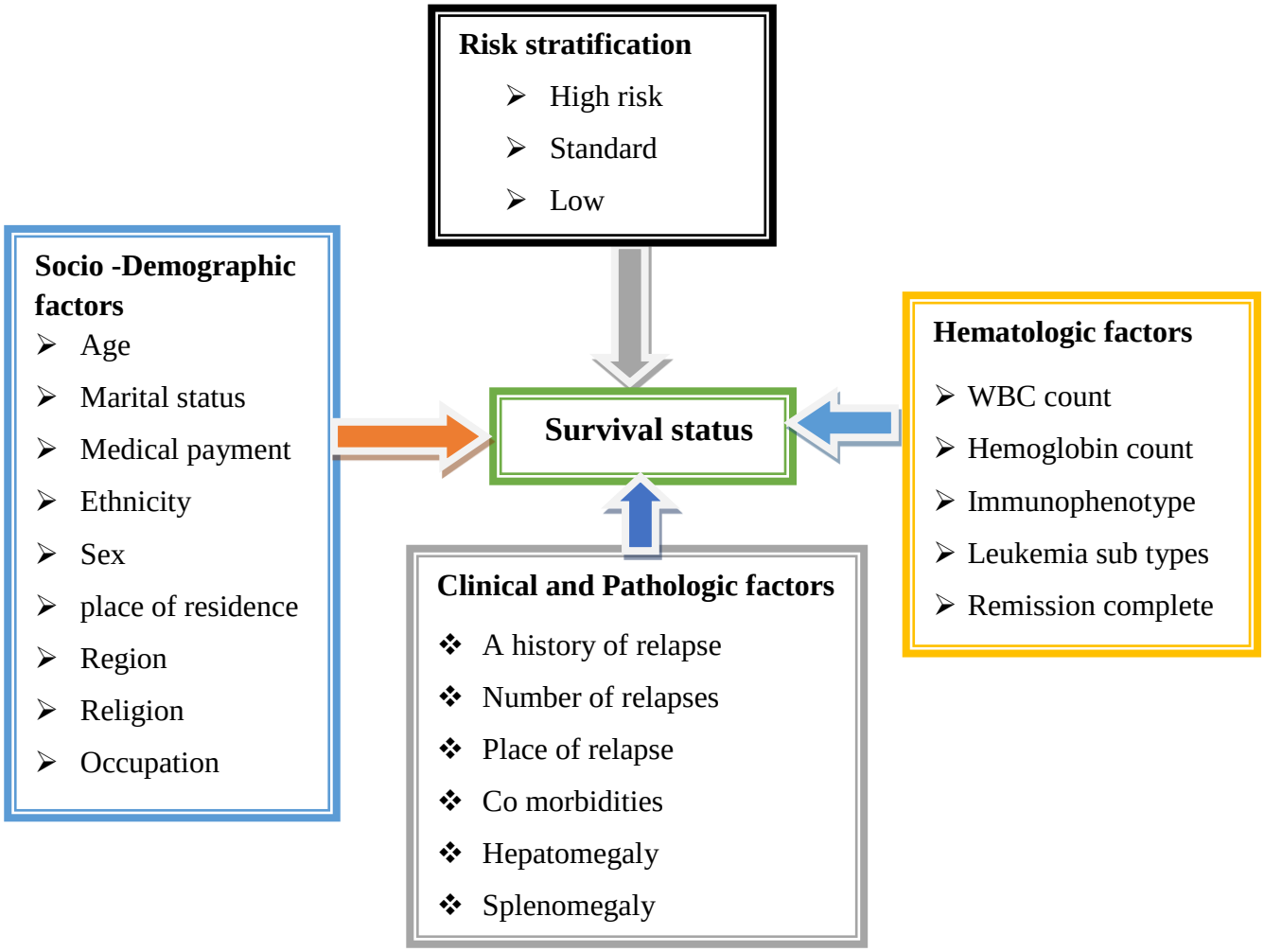

Figure 1: Conceptual frame that shows survival status of acute leukemia and predictors of mortality at TASH, 2019 EC (8, 11 and 26).

CHAPTER 3: OBJECTIVES

3.1 General objective

To determine survival status and predictors of mortality among acute leukemia patients attending adult hematology ward at Tikur anbessa specialized Hospital (TASH) Addis Ababa, Ethiopia,

3.2 Specific objectives

- To determine five year survival status of acute leukemia attending at TASH January 2014 up to December 2018, Addis Ababa, Ethiopia. .
- To identify predictors of mortality among acute leukemia patients attending at TASH January 2014 up to December 2018, Addis Ababa, Ethiopia.

CHAPTER 4: RESEARCH METHOLOGY

4.1 Study area and period

This study was conducted at Tikur anbessa specialized hospital (TASH) in Addis Ababa city administration which is capital city of Ethiopia between January 2014 to December 2018 among 119 participants. Addis Ababa is the largest and the populous city in the country. Total population based on world population review estimated growing closer to 4 million in 2017(46). Tikur Anbessa is the only government owned cancer center which serves for more than 105,350,020 population (47).

According to 2018 International network for cancer treatment report (INCTR) data, TASH has a total of 266, 975 patients annually, with 251,560 outpatients (43) but the hospital report was higher which is about 370,000- 400,000 patients per annum. The hospital has 600 beds, of which only 18 are dedicated for oncology patients. The hospital serves as the nation's sole cancer referral center providing chemotherapy, radiotherapy and palliative care for patients. In TASH oncology unit there were six senior oncologists, one palliative care specialist, two are hematologists, two pediatric oncologists, five radiotherapists, four medical physicists and two oncology nurses specialist working in oncology unit. Treatments offered at Tikur Anbessa specialized hospital cancer center include anticancer drugs, surgery, and radiotherapy. This study was taken place at the hematology ward which was one of the specialty units of the hospital(43).

4.2 Study design:

An institution based retrospective cohort study was conducted between March and April 2019GC.

4.3 Study population and source population

4.3.1 Source population

All acute leukemia patients admitted in the hematology unit of TASH Addis Ababa, Ethiopia

4.3.2 Study population

All acute leukemia patients aged above 12 years old admitted in the hematology unit of TASH Addis Ababa, Ethiopia from January first 2014 to December 31, 2018.

4.3.3 Study subject

All acute leukemia patients aged above 12 years old admitted in the hematology unit of TASH Addis Ababa, Ethiopia from January first 2014 to December 31, 2018 who fulfills the inclusion criteria.

4.3.4 Eligibility

Inclusion Criteria: All patients aged above 12 years diagnosed with acute leukemia, those diagnosed and started treatment.

Exclusion Criteria: A patient where data was incomplete and diagnosed with other type of acute leukemia rather than ALL and AML subtypes were excluded from the study, patients with other type of cancer.

4.4 Sample size determination

All patients (203) diagnosed with acute leukemia (107 ALL and 96AML) in survey were included in the study

4.5 Sampling technique procedure

All charts of patients diagnosed with acute leukemia by were conveniently included in the study, since the total population was lower than required sample size. Charts were selected using medical record numbers from hospital records (HMIS)

4.6 Operational definitions

Acute leukemia: diagnosis of AML and ALL during chart review was considered as acute leukemia in this study.

The follow-up time is documented as the duration from the time of diagnosis to death from any cause or the last day of the available.

Complete remission: is defined as the reduction of BM blasts to less than 5% with recovery of peripheral blood counts.

Induction death: death that occurs in first 30 days of treatment starts which mainly due to drug toxicity.

Overall survival: measured from the date of treatment until death from any cause for all patients. Patients who are still alive were censored at the last follow up date.

Normal hemoglobin means that admission hemoglobin greater than 11.

Censored: those participants whose true survival time (failure time) was not known because of the study ends or because a participant drops out of the study before experiencing the event.

4.7 Data collection methods

A data was extracted by using extraction sheet which was prepared in English. The extraction sheets consisted two parts. The first part contains general information including socio demographic characteristics of the subjects. The second part contains hematologic and pathologic factors. Three BSc nurses were recruited to collect data and one lecture (MSc nurse)supervised the whole process of data collection.

Data extracted from the case files/charts included socio demographic characteristics, diagnosis, duration of hospitalization, sex, place of residence, treatment, type of leukemia, a history of relapse, location and number of relapses, comorbidity, hemoglobin, white blood cells (WBCs), as well as hepato-splenomegaly, were inquired from the patients' medical records, physician reports, insurance agency records ,socio-demographic/SES. All laboratory data was from the time of diagnosis and outcomes (death, recovery, referral or unknown).

4.8 Study Variables

4.8.1 Dependent Variables

Survival status

4.8.2 Independent Variables

Age, medical payment, ethnicity, sex, place of residence, hemoglobin count, Immunophenotype, history of relapse , number of relapses ,place of relapse, comorbidities, induction response , WBC count Leukemia sub types, remission completeness, risky classification, hepatomegaly and splenomegaly.

4.9 Data quality control

To ensure the quality of the data the following measures were taken. The questionnaire was adapted from different articles with some modification (8) and (11) and checked by oncology experts (nurses and physicians) weather the adapted questioner measure the expected goal**.** After feedback from experts, necessary amendments were made accordingly. A total of one

day intensive training was given for supervisor and data collectors. The training focused mainly on the aim of the study and the data extraction tool, need of data completeness, confidentiality, and how to approach data extraction during the data collection process. Data was check on daily bases for its completeness, clarity and consistency by the supervisor and the principal investigator. Overall activity was controlled by the principal investigator.

4.10 Data processing and analysis

Collected data were checked at the end of each data collection day for its completeness and consistency. Analyses were based on 5-year survival rates. Data were edited, coded and entered to Excel. Finally, data were exported to SPSS version 25.0(IBM corp., Armonk, NY, USA) for analysis. Descriptive statics such as median, frequency mean and standard deviation were used to summarize the characteristics of the cohort.

Survival rates estimated by applying the Kaplan–Meier Log-rank model to estimate the survival time of leukemia patients based on explanatory variables. Bivariate and multivariate Cox proportional hazards regression models was performed to identify the associated factors of mortality. Variables that were statistically significant in bivariate analysis ($p<0.25$) was included in the multivariate Cox regression model to identify independent predictors of mortality and to estimate adjusted hazard ratios. Both crude hazards ratios and adjusted hazards ratio with 95% confidence interval were reported for variables that were statistically significant considered predictors of mortality among the study participants.

4.11 Ethical considerations

Ethical clearance was obtained from research and ethics committee (REC) of School of Nursing and Midwifery of College of Health science, Addis Ababa University. A written permission letter to access patient's charts (data) was obtained from TASH outpatient director directorate.

4.12 Dissemination of results

The result of this thesis was disseminated or communicated to Addis Ababa University School of Nursing, TASH, other concerned bodies through reports and publication on an appropriate journal.

4.13 Limitations of the Study

Design retrospective goes with past and no way to control the quality of past measurement. There were literature gaps in the topic in developing country and Africa which limited to compare current finding with developed country in more.

CHAPTER 5: RESULTS

5.1 Result

5.1.1 Socio-demographic characteristics of the study participants

A total of 203 acute leukemia patients have been seen from January 2014 to December 2018 in TASH from this 119 patient charts were eligible for this study. Eighty four charts were excluded from study due to incompleteness of study variables. The age range of this study starts from12 years and the Mean age was 40.5(SD±20.5) with minimum 13 and maximum 88 and the median age of the respondent was 39 ±20.5 years. Regarding to their religious 53(44.5%) respondents were Orthodox, 40(33.6%) were Muslim and 23(19.3%) were protestants. More than half of study participants were from Oromia and Amhara (28.6 and 25.2) regions respectively and greater than 60% of participants were rural inhabitants. Nearly half 60(50.4%) were married and 36(30.3%) were farmers. (Table1)

Table 1: Baseline Socio demographic characteristics of acute leukemia patients in TASH adult hematology oncology unit from January 2014_december 2018, Addis Ababa, Ethiopia 2019(n=119).

Characteristics	Categories	Status at last contact		Total
		Death	Censored	
Age category	12-34	13(24.1%)	41(75.9%)	54(45.4%)
	35-64	16 (39%)	25 (61%)	41(34.5%)
	>=65	17(70.8%)	7(29.2%)	24(20.1%)
Residence	Rural	21 (35%)	39(65%)	60(50.4%)
	Urban	25(42.4%)	34(57.6%)	59(49.6%)
Marital status	Married	23(38.3%)	37(61.7%)	60(50.4%)
	Single	16(34.8%)	30 (65.2%)	46(38.8%)
	Divorced	7(63.6%)	4(36.4%)	11(9.2%)
	Widowed	0	2(100%)	2(1.6%)
Sex	Male	26(41.3%)	37(58.7%)	63(52.9%)
	Female	20(35.7%)	36(64.3%)	56(47.1%)
Ethnicity	Amhara	16(39%)	25(61%)	41(34.5%)
	Oromo	10(30.3%)	23(69.7%)	33(27.7%)
	Tigre	12(54.5%)	10(45.5%)	22(18.5%)

	Others	8(34.8%)	15(65.2%)	23(19.3%)
Occupation	Farmer	25(56.8%)	19(43.3%)	44(36.9%)
	Merchant	21(48.8%)	22(51.2%)	43(36.6%)
	Civil servant	17(62.9%)	10(38.1%)	27(22.6%)
	NGO	3(0.6%)	2(0.4%)	5(4.2%)
Religion	Orthodox	32(60.4%)	21(39.6%)	53(44.5%)
	Muslim	24(60%)	16(40%)	40(33.6)
	Protestant	11(47.8%)	12(52.2%)	23(19.3%)
	Catholic	2(66.7%)	1(33.3%)	3(2.5%)
Region	Oromia	14(41.2)	20(58.8%)	34(28.6%)
	Amhara	10 (34.5%)	19(65.5%)	29(24.4%)
	SNNPR	8(38.1%)	13(61.9%)	21(17.6%)
	Tigrey	9(19.6%)	4(5.5%)	13(10.9%)
	AA	4(22.2%)	14(19.2%)	18(15.1%)
	Somalia	1(25.0%)	3(75.0%)	4(3.4%)

5.1.2 Hematologic and pathologic characteristics

Near to half of study participants were diagnosed with AML 62(52.1%) subtypes, among ALL subtypes B-immunophenotype were predominant groups 38(68.4%). More than half of a participant did not achieve complete remission during survey period 60(50.4%). Majority of respondents were self-paid for medical payment 77(64.7%). Around 27(22.7%) of participants developed relapse during survey period among this central nervous system were common place for relapse 15(55.6%) shown below table 2.

Table 2: Hematologic and pathologic characteristics of acute leukemia patients at TASH Addis Ababa, Ethiopia from January 2014 to December 2018 (n = 119).

Covariates	Categories	Status at last contact		Total
		Death	Censor	
Acute leukemia subtypes	AML	27(43.5%)	35(47.9%)	62(52.1%)
	ALL	19(33.3%)	38(66.7%)	57(47.9%)
ALL Immunophenotype	B	12(30.8%)	27(69.2%)	39(68.4%)
	T	7(38.9%)	11(61.1%)	18(31.6%)

Hemoglobin	Abnormal	19(34.5%)	36(65.5%)	55(46.2%)
	Normal	27(42.2%)	37(50.7%)	64(53.8%)
WBC	≤10,000	0	26(35.6%)	26(21.8%)
	10,000-50,000	13(28.9%)	32(43.8%)	45(37.8%)
	≥50,000	33(68.8%)	15(20.5%)	48(40.3%)
Phase of chemotherapy	Induction	18(62.1%)	11(37.9%)	29(24.4%)
	Consolidation	18(60.1%)	12(40%)	30(25.2%)
	Maintenance	21(56.8%)	16(43.2%)	37(31.1%)
	Complete	12(52.2%)	11(47.8%)	23(31.1%)
Aim of treatment	Radical	37(40.7%)	54(59.3%)	91(76.5%)
	Palliative	9(32.1%)	19(67.9%)	28(23.5%)
Medical payment	Self	30 (39.0%)	47 (61.0%)	77(64.7%)
	Public	14 (35.9%)	25 (64.1%)	39 (32.8%)
	Others	2(66.7%)	1(33.3%)	3(2.5%)
New cancer	Yes	7(31.8%)	15(68.2%)	22(18.5)
	No	39(40.2%)	58(59.8%)	97(81.5%)
Complete remission	Yes	6(24%)	19(76%)	25(21%)
	No	40(43%)	53(57%)	93(78.8%)
Splenomegaly	Yes	30(50%)	30(50%)	60(50.4%)
	No	16(27.1%)	43(59.7%)	59(49.6%)
Hepatomegaly	Yes	34(64.2%)	19(28%)	53(44.5%)
	No	12(18.2%)	54(81.8%)	66(55.5%)
Relapse	Yes	22(81.5%)	5(18.5%)	27(22.7%)
	No	24(26.1%)	68(73.9%)	92(77.3%)
Place of relapse	BM	4(57.1%)	3(42.9%)	7(29.9%)
	CNS	14(93.3%)	1(6.7%)	15(55.6%)
	BM and CNS	4(80%0	1(20)	5(18.5%)

Table 2 continued to next page

Number of relapse	1	6(66.7%)	3(33.3%)	9(33.3%)
	2	9(81.8%)	2(18.2%)	11(40.7%)
	≥3	7(100%)	0	7(25.9%)
Comorbidity	Yes	21(75%)	7(25%)	28(23.5%)
	No	25(27.5%)	66(72.5%)	91(76.5%)
Comorbidity types	Sepsis	8(66.7%)	4(33.3%)	12(44.4%)
	Nutrophinic fever	10(76.9%)	3(23.1%)	13(48.1%)
	Others	1(5.3%)	1(12.5%)	2(7.4%)
Death in 30 days	Yes	6(53.8%)	0	6(5%)
	No	40(35.4%)	73(64.6%)	113(95%)

5.2 Incidence and overall Survival of acute leukemia patients during the follow-up time

Total of 119 acute leukemia patients were followed for 60 months or five years with yielding 196years-time at risk. Forty six (38.7%) new death were observed in the total follow up time making the overall death incidence rate 23.5 (95% CL: 18-52) per 100 person-years.The median survival of this cohort was 35 months (95% CI, 28.3-41.7) and the median follow up time is 17(95% CI, 1-59) months. Overall estimated survival rate after treatment of acute leukemia was 21 % at 60 months of follow up.

The estimated cumulative survival was 89.1 %,67.7 %,44.4%,28.5 %,21 % at 12, 24, 36, 48; 60 months respectively as shown on the following Kaplan Meir survival curve (Figure 2). The curve also indicates that the probability of survival decreases as the follow-up time increases which was the typical characteristics of survival data analysis. As it is also clearly shown on the KM survival curve, the highest rate of mortality was observed between 12-36 months. Figure6 below shows that overall Kaplan-Meier estimation of survival functions of acute leukemia patients followed at TASH, Addis Ababa, Ethiopia, from January 2014 to December 2018.

Graph below in figure 2 shows that overall survival curve which slops down with increased age.

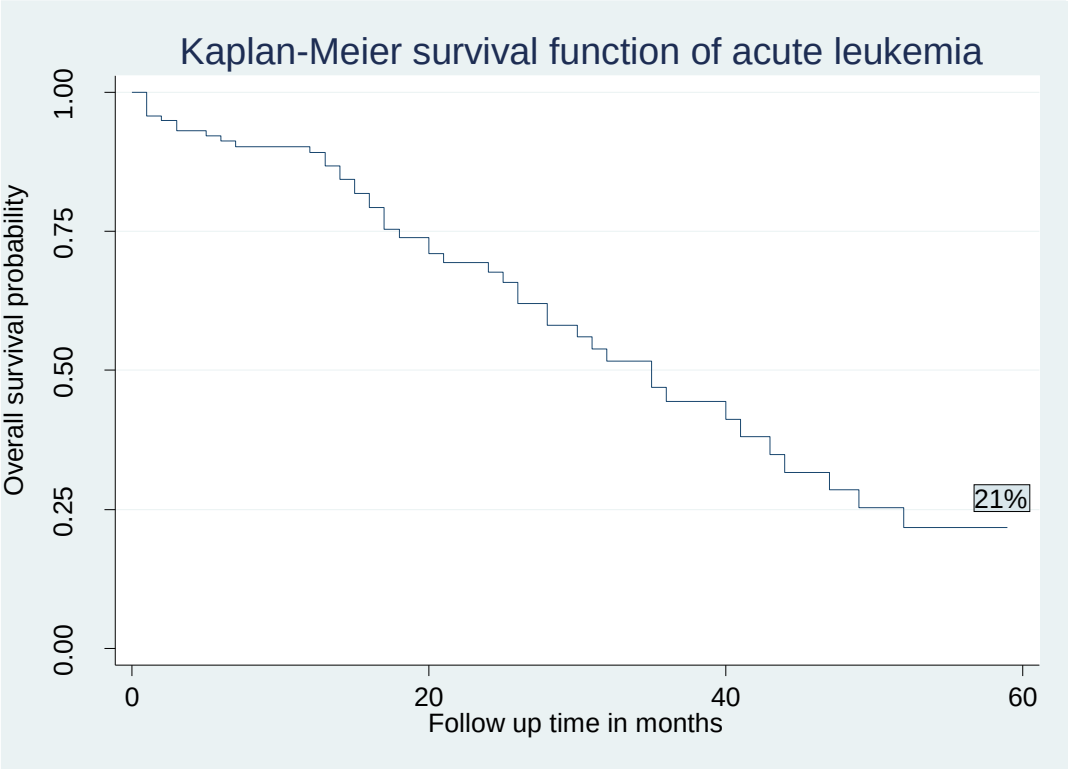

Figure 2: Overall Kaplan-Meier estimation of survival functions of acute leukemia patients followed at TASH, Addis Ababa, Ethiopia, from January 2014 to December 2018.

5.3 Survival experience among different groups of leukemia patients in log rank test

Log-rank test was performed to test equality of survival curves for the presence of any significant differences in survival time among various levels of the categorical variables considered in the study. Statistical difference in survival time between different categories of covariates was tested. It was found that there is a significant difference in survival experience between categories of leukemia subtypes, age, comorbidity, and relapse.

Table 3 shows that the median survival time for those who ALL subtypes had a longer survival time than those AML subtypes (43 months) (95% CI: 37.91-48.08) <0.02)). The median survival time for those who have no any comorbidity had better survival time (47 months (95% CI: 28.30-41.69) p=0.00)) than those who have any type of comorbidity.

Patients with history of hepatomegaly have a lower medial survival 28(95%CI:20--35.9)) than those who have no history of hepatomegaly. Those who have history of relapse leukemia have worsened median survival 20 months in relation with non-relapse 23 months (95% CI: 14.82-31.17) P=0.00)). Those who have younger age (<34) have better survival with median survival of 44 months than those with higher age greater 65 than 49(95% CI: 14.6-54, P< 0.017).

Table 3: Median survival time, cumulative survival probability and log rank test according to different characteristics of patients during 5-year of follow-up (Kaplan-Meier method) of acute leukemia at TASH, A.A Ethiopia (n=119)

Variables	**Median survival time, in month (95% CL)**	**Overall 5-year Survival (%)**	**Log rank test**	**p–value**
AL subtypes			9.26	0.02
AML	25 (95% CI:18.28-31.71)	19.4		
ALL	43(95% CI:37.91-48.08)	27		
Relapse			27.14	0.00
Yes	20(95% CI:13.21-26.78)	0		
No	23(95% CI:14.82-31.17)	35.6		
Age			2.31	0.017
12-34	49(95% CI :14.6-54)	49.9		
35-64	31(95% CI:16.35-47.4)	9.9		
≥65	17(95% CI: 2.28-31.71)	0		

Table 3 continued to next page

Hepatomegaly			7.09	0.008
Yes	28(95%CI:20--35.9)	15.3		
No	47(95%CI:27.7-60	34.3		

Comorbidity			26.01	0.00
Yes	20(95% CI:16.57-23.42)	0		
No	47(95% CI:28.30-41.69)	34.4		

5.4 Graphical presentation of different categories in Kaplan-Meier analysis

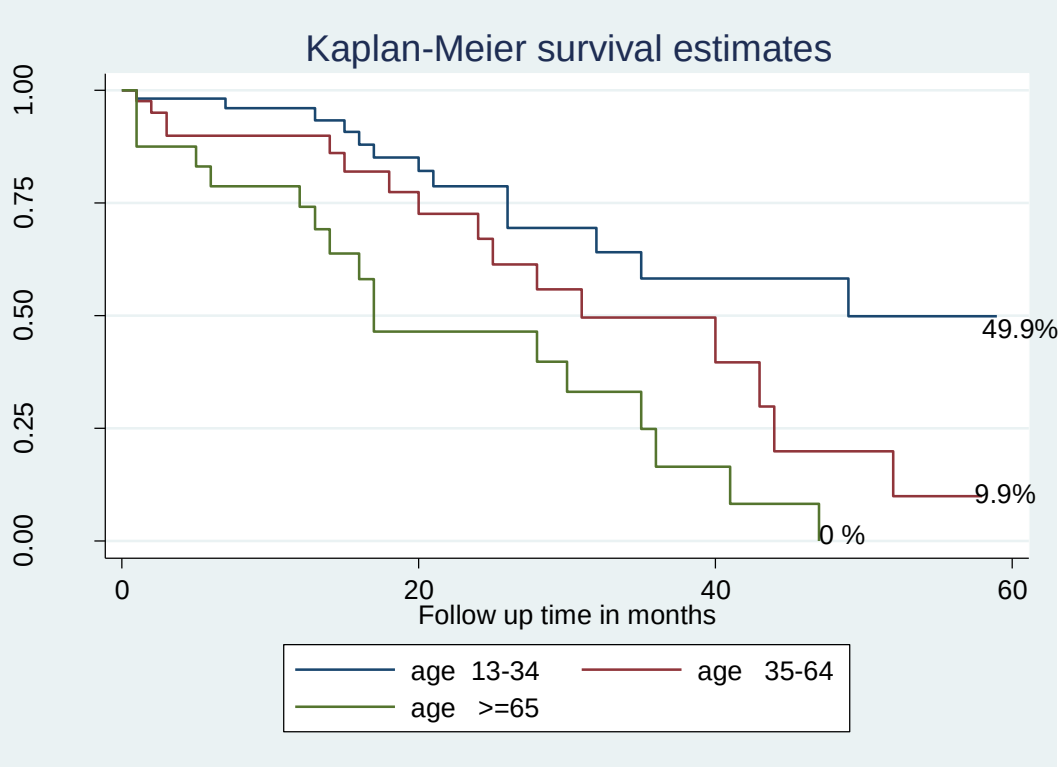

Figure 3: survival status in relation with age categories in TASH, Addis Ababa, Ethiopia from January 2014 to December 2018(n=119).

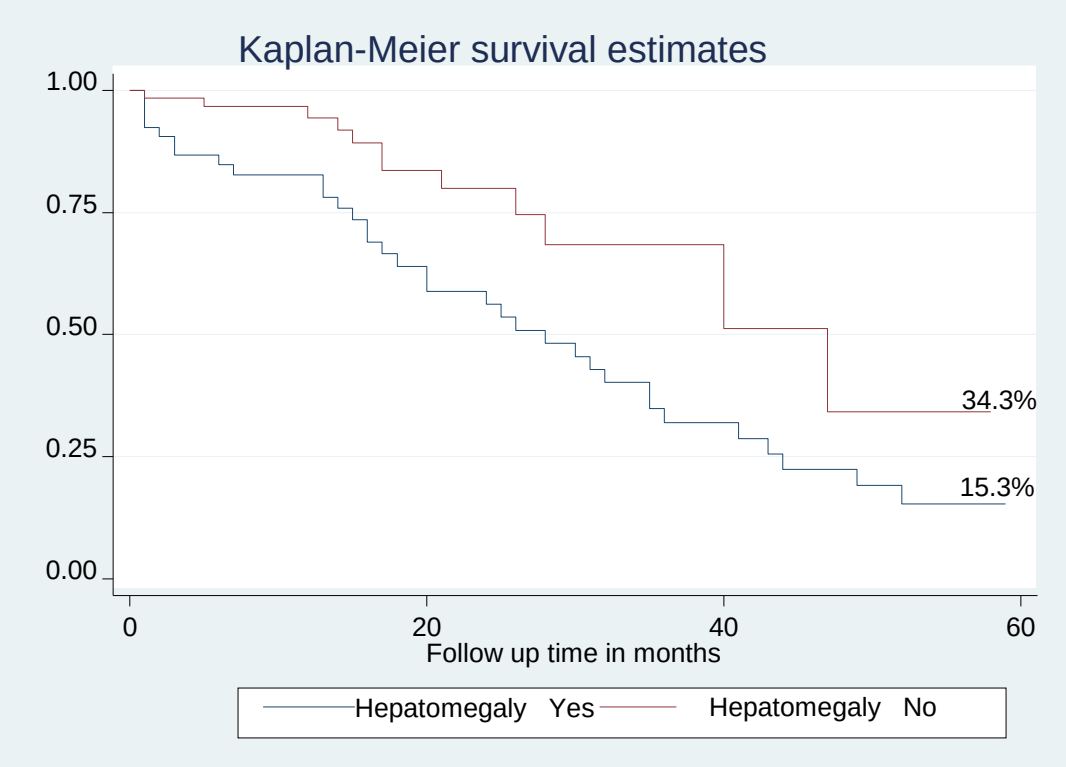

Figure 4: Kaplan-Meier survival curves comparing survival time of hepatomegaly absence or presence with relation to survival in TASH, Addis Ababa, Ethiopia from January 2014 to December 2018(n=119).

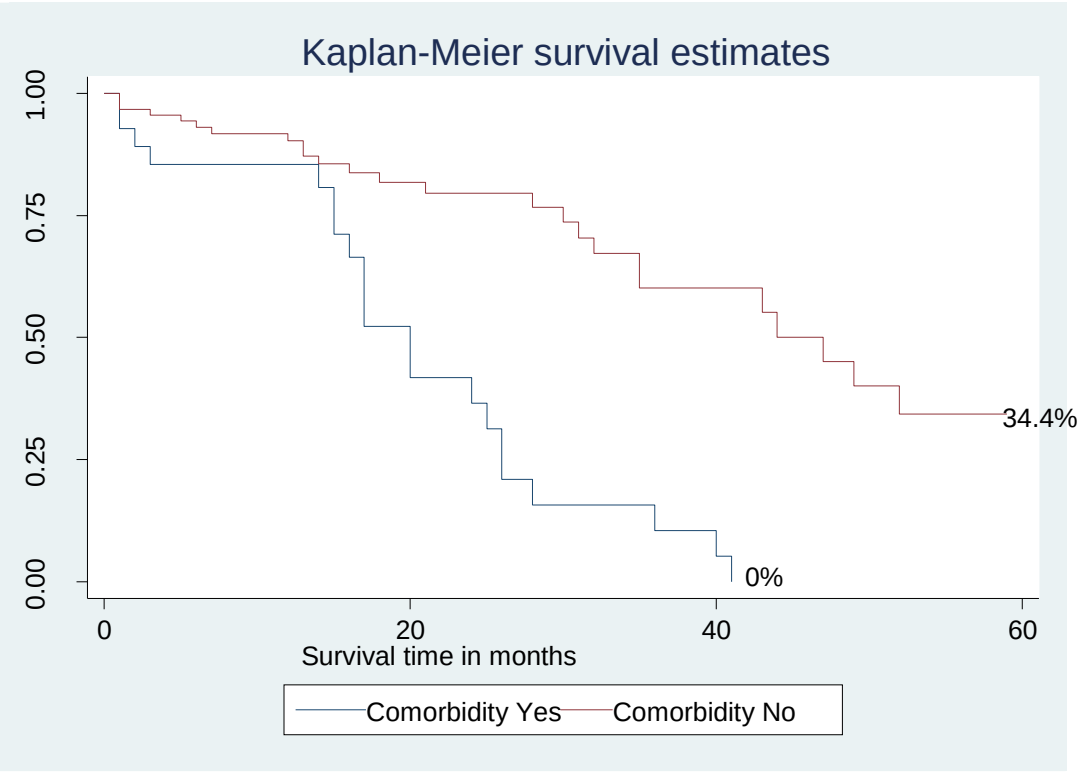

Figure 5: Survival status with either presence or absence of comorbidity; those with any comorbidity have lower survival with relation with no comorbidity TASH, Addis Ababa ,Ethiopia from January 2014 to December 2018(n=119).

From the curve below it can be seen patients with ALL subtypes diagnosed where better survival than patients with AML subtypes.

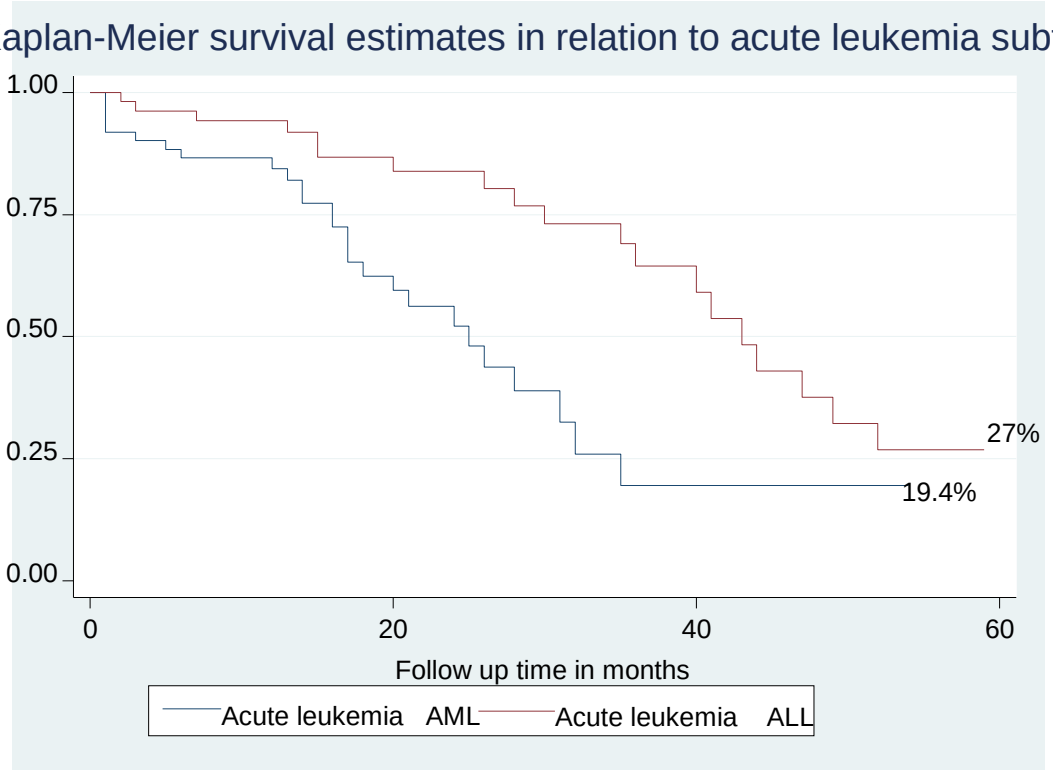

Figure 6:The Kaplan-Meier survival curves compare survival time of acute leukemia patients relation of AML to ALL subtypes TASH, Addis Ababa ,Ethiopia from January 2014 to December 2018(n=119).

The Kaplan-Meier graph below shows that median survival time for those who have relapse was lower than 20(95% CI: 13.21-26.78) those who have no relapse history 23(95% CI: 14.82-31.17) P=0.00) shown in figure below.

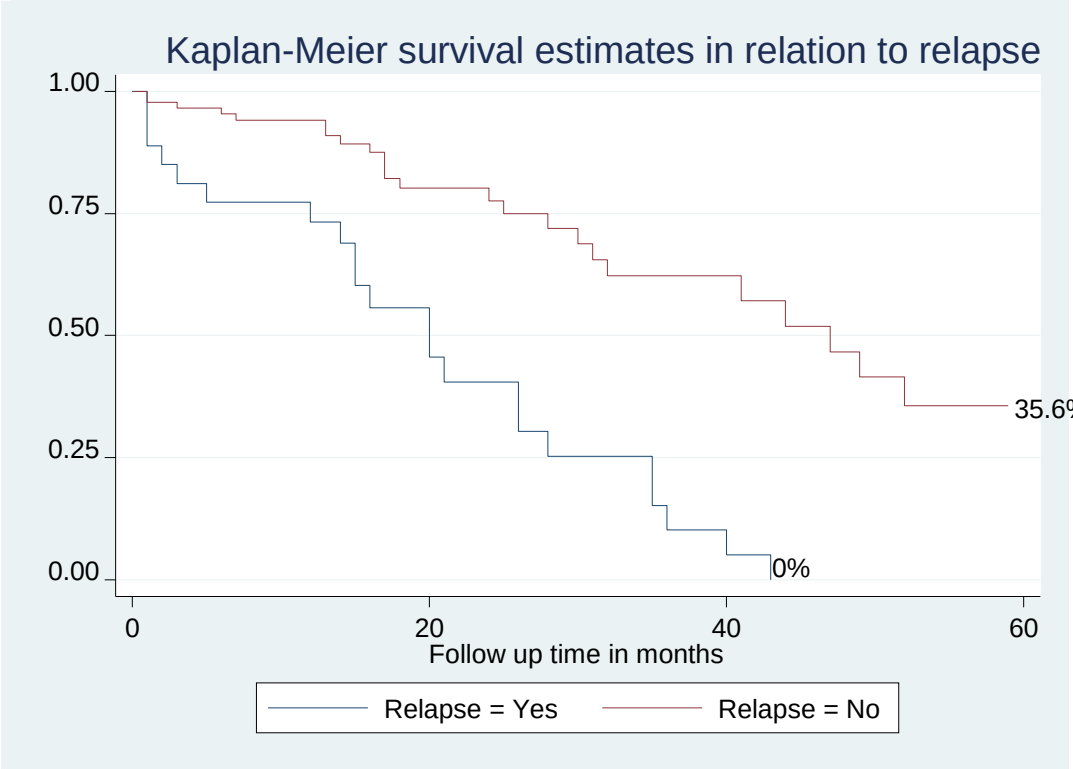

Figure 7 :-The Kaplan-Meier survival curves comparing survival time of relapse patient's status at TASH, Addis Ababa, Ethiopia from January 2014 to December 2018(n=119).

5.5 Modeling of risk factors which are effective in the leukemia survival rate by using Cox regression model

The table 4 below shows results from bivariate Cox regression analysis showed that: type of leukemia subtypes (HR:2.5, 95%CI:1.36-4.68), age (HR:0.27,95%CI; 0.12-0.5) comorbidity(HR:4.4,95%CI:2.34-8.1), hepatomegaly (HR: 2.4, 95% CI: 1.2-4.6), history of relapse(HR:4.4,95%CI: 2.37-8)and splenomegaly (HR: 2.08, 95% CI:1.13-3.83)were candidate variables for multiple Cox regression model at p-value <0.25 then covariates were adjusted to multivariate analysis to identify strength of association with cut point p-value 0.05. This above all variables are manipulated to multivariate Cox regression, then acute leukemia subtypes (HR: 4.9, 95% CI: 2.3-10.4,P value <0.00), history of relapse (HR: 3.9, 95%CI: 1.0-7.9, P< 0.002), age (HR:1.25,95% CI: 1-1.75,p<0.01),Hepatomegaly(HR:2.7,95%

CI:1.36-5.36, p<0.004) and splenomegaly(HR:2.29 95% CI: 11.2-4.4 ,p<0.014 were the major predicting factors of acute leukemia death shown in table 4.

Table 4: Bivariate and multivariate Cox regression analysis of acute leukemia in study population at TASH, Addis Ababa, Ethiopia from January 2014 to December 2018(n=119).

		Crude hazard rate		adjusted hazard rate			
Variables	Covariate			HR	CI 95	HR	CI 95%
		Death	Censored				
Leukemia	AML	27(43.5%)	41(75.9%)	2.5	1.36-4.68	4.9	2.3-10.4
	ALL	9(33.3%)	35(47.9%)	Ref			
Relapse	Yes	22(81.5%)	5(18.5%)	4.4	2.3-8.	3.9	1.0-7.9
	No	24(26.1%)	68(73.9%)	Ref			
Comorbidity	Yes	21(75%)	7(25%)	4.4	2.34-8.1	1.6	0.8-3.3
	No	25(75%)	66(72.5%)	Ref			
Splenomegaly	Yes	30(50%)	30(50%)	2.08	1.13-3.83	2.29	1.2-4.4
	No	16(27%)	43(73%)	Ref			
Hepatomegaly	Yes	34(64.2%)	19(28%)	2.4	1.2-4	2.7	1.36-5.4
	No	12(18.2%)	54(81.8%)	Ref			
Age	12-34	13(24.1%)	41(75.9%)	Ref			
	35-64	16 (39%)	25 (61%)	0.27	0.24-0.95	0.6	0.3-1.4
	≥64	17(70.8%)	17(70.8%)	0.4	0.12-0.5	1.25	1-1.75

* p<0.25 and **p< 0.05

CHAPTER 6: DISCUSSION

The overall survival of acute leukemia in the developed world was high, while it was very low in developing countries indicating that the center for cancer management/treatment in the developing countries is very young for some leukemia types (12).In this study, the survival rate for patient with acute leukemia was 21%. This was lower than the rates reported from other developing countries which was reported 86% in India(23), and 52% in Nigeria (8). The variation may be due to the fact that patients in the current study area may lack access to early treatment because there is single cancer center in the country. Overall survival of AML was (19%) which is almost similar with the study in USA which showed 18.2% but for ALL the current finding found27 % which was lower than USA 44.0%(21).

The current study found a higher value in induction death (13%)in relation to US finding 10% induction deaths which is suggestive indicator for regimen difference or low cytotoxicity management and complete remission rate was very low (21%) in current study compared to the American study which was around 57% in(22). Overall survival of both types of acute leukemia showed lower survival rate in comparison with the Canadian study which reports ALL and AML patients (64%) and 62%) respectively(25), which is probably due to poor or luck of medical management for advanced tumor in the existing set up. In the current study subtypes of leukemia, history of relapse hepatomegaly, splenomegaly and age were major predicting factors for acute leukemia mortality in TASH.

According to the current findings survival of AML (19%) sub types were found to have lower survival in relation to ALL (27%) subtypes which is consistent with the report by American cancer association which showed survival of AML (66%) lower survival than that of ALL (90%)(20). Another study done in Nigeria was also congruent with the current finding that ALL (77.7%) with a better survival than AML (44%) sub types(8). In this study, no significant association was found between WBC count and survival of leukemia cases, however, the study conducted in USA implicated that higher WBC count ($\geq$ 50,000/μL) results in poorer outcome (41). History of relapse was found to be one of the predicting factors of survival of acute leukemia, the finding is similar with the study in Britain which

indicated relapse history, site of relapse and number of relapse as the major predictors of acute leukemia death (27).

Age at diagnosis was one of the risk factor affecting survival in leukemia cases. Those leukemia patients aged greater than 65 were found to have a higher risk of mortality as compared to those aged less than 34. The result was supported by UK study where clients aged less than 34 years demonstrated a better survival(33). This study also showed that worsen survival among age group >64 years the current findings also have similar finding increased age have (>64) have a worse survival (33). The finding was also supported by the Canadian study which showed that age at diagnosis is linked with survival of acute leukemia cases in which older ages are at a higher risk for death in comparison to the young ones (5). ASCO finding reports that age > 40 years 2.2 times hazards of death in relation with (≤ 40) years(29) the current finding also in line with it in which older age(>64) was 1.25 hazards of death in comparison with age <34 years.

A study in the US also showed that leukemia subtype and sex are the determinant factors for survival in leukemia cases. The study indicated that, female patients with the diagnosis of leukemia had a better survival rate than male patients. The study also reported that, survival declined in successive age groups above 45 to 54 years in all leukemia subtypes(21), but in the current study, no association was found between sex and survival status among acute leukemia cases. The five year survival of acute leukemia decreases with advanced age groups, which is consistent with reports from other studies indicating that the five year survival of acute leukemia patients approaching to 40% in younger patients and 15% in older adults(30).

Acute leukemia, generally defined by age ≥60 years, has worse treatment outcomes than younger patients and has poor survival. This disparity may be due to biologic characteristics (32) the current study also agrees with this variation may be due to biological characteristic's. The result of this study showed that leukemia patients who have hepatomegaly was 2.7 hazards and splenomegaly was 2.29hazards of death in relation with those who have no history of hepatosplenomegaly which was supported by Iranian finding (39). Current finding showed that splenomegaly have a great significance of leukemia survival which is supported by reports of American hematology society(40)

CHAPTER 7: CONCLUSSUION AND RECOMANDATION

7.1 Conclusion

Survival status of acute leukemia cases in this study was very low. Advanced age, history of relapse, hepatomegaly, splenomegaly and leukemia subtype are determinant factors for acute leukemia. History of relapse, hepatomegaly, splenomegaly are typical features of advanced leukemia and it may be due to delayed diagnosis and treatment, so Strengthening cancer care centers, improving community awareness, timely diagnosis and treatment may be necessary to increase patient survival. Increased age have greater risk for leukemia death so advanced age needs special care for acute leukemia.

7.2 Recommendation

Survival rate of acute leukemia patients in this study was very low as compared to other studies conducted in the developing as well as developed world. The problem requires attention from all stake holders.

FMOH:

- ✓ Should give emphasis for expanding and capacitating leukemia care centers
- ✓ Capacitating health care providers working in the leukemia care centers and adequate resource allocation to modify survival of acute leukemia.

Hospital:

- ❖ Early detection and treatment of cases to improve survival rate of leukemia cases and increasing community awareness may be essential component to improve patient's prognosis.
- ❖ Hospitals should focuses on advancing treatment modalities including bone marrow transplant, gene therapy and others advanced modalities.

Researchers:

- Further studies exploring factors for poor survival of among acute leukemia patients may be necessary to design new strategies for increased survival of patients.
- Socio-economic and genetic factors also suggested due to variation may socioeconomic or biological/genetic.

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CHAPTER 9: ANEXES

A: Information sheet

Title of the research thesis: Survival status and predictors of mortality among acute leukemia patients attending adult hematology unit at Tikur Anbessa Specialized Hospital Addis Ababa, Ethiopia.

Name of Investigator: Bargude Balta

Name of the Organization: Addis Ababa University, College of Health science, school of Nursing and midwifery, department of nursing.

Name of the Sponsor: Addis Ababa University

Introduction: this information sheet is prepared for Tikur Anbessa Specialized Hospital, hematology oncology unit Addis Ababa, Ethiopia. The aim of the form is to make the above concerned office clear about the purpose of research, data collection procedures and get permission to conduct the research.

Purpose of the Research thesis: To assess survival status and associated factors of death among acute leukemia patients follow up at black lion specialized hospital adult hematology oncology unit, Addis Ababa, Ethiopia, 2019.

Procedure: In order to achieve the above objective, information, which is necessary for the study, was taken from acute leukemia medical record follow up forms, chemotherapy intake forms, radiation therapy chart and medical history sheet. In order to come up with the above mentioned findings, total document of program clients enrolled during January 1st 2014 to December 31th 2018 was selected and followed up and a review of the required information from the records will be made by using the checklist. There will be a phone call to patients to collect information on some variables.

Risk and /or Discomfort: Since the study was conducted by taking appropriate information from medical chart, it will not inflict any harm on the patients.

The name or any other identifying information was not be recorded on the questionnaire and all information taken from the chart was kept strictly confidential and in a safe place. The information extracted was kept secured by locked in to locker by key.

After the data was entered in to the computer by password, the information retrieved was only used for the study purpose.

Benefits: the research has no direct benefit for those whose document/ record was included in this research. However, the indirect benefit of the research for the participant and other clients in the program is clear. This is because if program planners are preparing predicted plan, there was a benefit for clients in the program of getting appropriate care and treatment services for the leukemia patients. Of all, the research work has a paramount direct benefit for health care planners and managers, especially for those on leukemia program planning and management.

Confidentiality: To ensure confidentiality the data on the chart was collected by those individuals who were professional nurses and information was collected without the name of the clients. The information collected from this research project was kept confidential and will be stored in a file. In addition, it will not be revealed to anyone except the investigator and it was kept in key and locked system with computer password.

Person to contact: This research project was reviewed and approved by the institutional review board of college of health sciences, school of nursing and midwifery, Addis Ababa University. If in case you want to know more information about the research and its undertakings, you can contact the committee through the address below.

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Permission: Lastly but not least, you are kindly requested to permit and forward your permission to concerned body in your organization so that the researchers can get cooperation from the data clerks and other responsible bodies in place.

B: Data extraction form

Table 5: Data extraction form for the assessment of survival and factors associated with death of adult Leukemia patients attending adult cancer therapy at TASH, Addis Ababa, Ethiopia, 2019(n=119).

Part I: Socio-demographic characteristics			
S.No	Variable Category	Code	Remark
01.	Patients medical Number	-------	
02.	Age in years	_____in years	
03.	Residence of patients	1.Urban 2.Rural	
04.	Marital status	1. Married 2. Single 3 Divorced. 4. Windowed	
05.	Sex patients	1 Male 2 Female	
06.	Region	1.Oromiya 2. Amhara 3. SNNPR 4. Tigray 5. Addis Ababa 6. Somale	
07.	Ethnicity	1 Oromo 2 Amhara 3 Tigray 4. Others(specify) _____	
08.	Occupation	1.Farmer 2.Marchant 3.Civil servant 4. NGO	
09.	Religion	1.orthodox 2.muslim 3.protestant	

		4. Others (specify….)	
010.	Medical payment	1 Self pay 2 At public expense 3 Medical insurance 4 others	
011.	Date diagnosed EC	DD/MM/YY	
012.	Date of treatment started	DD/MM/YY	
013.	Phase of chemotherapy	1. Induction 2. Consolidation 3. Maintenance 4.All cycles complete	
014.	Date of last follow up in hospital in GC	DD/MM/YY	
Part I I:Hematologic and clinical factorsfactors			
015.	Diagnosed leukemia subtypes	1 AML 2 ALL	If AML skip to 18
016.	Immunophenotype if ALL	1 T-cell 2 B-cell	
017.	Risky stratification for ALL	1 Low, 2 Standard 3 high	
018.	Admission hemoglobin count(K/uL)		
019.	Admission Platelet count(K/uL)		
020.	Admission WBC count: (K/uL)		
Part III Clinical and pathologic factors			
021.	Any co morbidity	1 Yes 2 No	If no ,skip to q23
022.	If yes, for q24	1 Sepsis 2 Neutropenic fever 3 Malnutrition 4 Others specify_____	
023.	Relapses:	1. Yes 2. No	If no skip to q26
024.	If yes for q23 - number of	1. 1	

	relapses:	2. 2 3. ≥3	
025.	If yes for q23 Place of relapse If yes	1. Bone marrow (BM) 2. Central nervous system 3. BM-CNS 4. Peripheral blood 5. Others specify_____	
026.	Hepatomegaly	1.Yes 2.No	
027.	Splenomegaly	1. yes 2. No	
028.	Complete remission	1. Yes 2. No	
029.	New cancer during or after treatment	1 Yes 2 No	
030.	Aim of treatment	1. Radical 2. Palliative	
031.	Survey status at last session	1. Died 2. Treatment/follow up 3. Stopped treatment 4. Unknown 5. Transferred/referred	
032.	If died death occurred in before 30days of treatment	1. Yes 2. No	