ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF NURSING AND MIDWIFERY

OUTCOME OF PATIENTS WITH NON HODGKIN'S LYMPHOMA AND ITS PREDICTORS, AT TIKUR ANBESSA SPECIALIZED HOSPITAL: A RETROSPECTIVE CHART REVIEW; ADDIS ABABA, ETHIOPIA, 2019

BY: BRUKTAWIT TADESSE WAZA

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

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By my signature below, I declare and affirm that this thesis is my own work. I have followed all ethical principles of scholarship in the preparation, data collection, data analysis and completion of this thesis. All scholarly matter that is included in the thesis has been given recognition through citation. I affirm that I have cited and referenced all sources used in this document. Every effort has been made to avoid plagiarism in the preparation of this thesis.

This thesis is submitted in partial fulfillment of the requirement for a graduate degree from the Addis Ababa University at College of Health Sciences, School of Nursing and Midwifery. The thesis is deposited in the Addis Ababa University Digital Library and is made available to local, national and international scientific community. I solemnly declare that this thesis has not been submitted to any other institution anywhere for the award of any academic degree, diploma or certificate.

STUDENT

Name: Bruktawit Tadesse Waza Signature: _____ Date: _____

ACKNOWLEDGMENTS

First and foremost, I am thankful to God; his grace and provision have been sufficient in enabling me achieve this thesis. Then I would like to extend my sincere gratitude to my advisors Amsale Cherie and Debela Gela for their constructive comments. Addis Ababa University, College of Health Sciences, School of Nursing and Midwifery is gratified as well for giving me the opportunity to do this research. My appreciation also goes to the staff of health science library; hematology and oncology departments of Tikur Anbessa Specialized Hospital, friends and those helped me by collecting and analyzing data throughout this thesis.

LIST OF ACRONYMS

AUC	Area Under The Curve
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
DLBCL	Diffuse Large B-Cell Lymphoma
ECOG	Eastern Cooperative Oncology Group
ENKTL	Extra nodal Natural Killer/T-cell Lymphoma, Nasal Type
HM	Hematological Malignancies
LDH	Lactate Dehydrogenous
LMR	Lymphocyte-to-Monocyte Ratio
MZL	Marginal Zone Lymphoma
NHL	Non Hodgkin's Lymphoma
NLR	Neutrophil Lymphocyte Ratio
OS	Overall Survival
PC	Platelet count
PFS	Progress Free Survival
PLR	Platelet Lymphocyte Ratio
QOL	Quality of Life
R-CHOP	Rituximab plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
ROC	Receiver Operating Characteristic
TASH	Tikur Anbessa Specialized Hospital

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ABSTRACT

Background: Non- Hodgkin's Lymphoma is the common hematological malignancy, which originates from lymphatic and immune systems; including lymphocytes and lymph nodes. In Ethiopia Non- Hodgkin's Lymphoma, ranked as 5th most prevalent and 10th deadliest cancer, none the less there is lack of adequate information on the outcomes of patients with Non-Hodgkin's Lymphoma and its predictors.

Objective: this study aims to assess Outcome of patients with non Hodgkin's lymphoma and its predictors, at Tikur Anbessa Specialized Hospital: a retrospective chart review; Addis Ababa, Ethiopia, 2019.

Methods: Institutional based Retrospective Chart Review study was conducted among patients with Non- Hodgkin's Lymphoma admitted to Tikur Anbessa Specialized Hospital, Hematology unit. Population censes was used to extract data from 71 adult patient charts from February to April 2019. The data were coded and analyzed by using SPSS version 20 and Cox Hazard regression model was used to calculate the substantial association between the dependent and independent variables, while Kaplan–Meier Log-rank model was used to estimate the survival time of patients after Non- Hodgkin's Lymphoma diagnosis.

Result: A total of 71 patients were analyzed. The overall five year survival from Non-Hodgkin's Lymphoma was 32.1%with the median survival of 27 months, 95% CI, [21.98-32.01]. Advanced age, Neutrophil count, monocyte count and Lymphocyte count predicted the outcome of Non- Hodgkin's Lymphoma dependently on the bivariate analysis. While relapse, advanced stage, Charlson Comorbidity index ≥3, lymphocyte monocyte ratio <3.1, neutrophil lymphocyte ratio (>2.8), and elevated lactate ≥ 245 predicted mortality independently; whereas only platelet lymphocyte ratio ≥144 was found to be independent predictor of good prognosis on multivariate analysis.

Conclusions and recommendations: Generally, the prognosis of Non- Hodgkin's Lymphoma patents was found to be poor; compared to outcomes in the developed world. So, more emphasis should be given to non communicable diseases along with palliative and end of life care on the health policy.

Key words: Non- Hodgkin's Lymphoma, predictor, outcome

1. INTRODUCTION

1.1. Background

Non- Hodgkin's Lymphoma (NHL) is the common hematological malignancy, which originates from lymphatic and immune systems; including lymphocytes and lymph nodes(1). Non- Hodgkin's Lymphoma represents heterogeneous group of malignancies accounting for 90% of lymphoid malignancies, each having different etiologies, morphology, immuno phenotype, clinical feature and response to therapy. Depending on the type of cell the lymphomas arise, NHL is classified in to three types and each lymphoma types have different sub types. This are B- cell, T- cell and NK- cell lymphomas. B cell lymphomas are by far the commonest type of lymphoma in the western world with the prevalence of 90% over all lymphomas, while T-cell lymphoma accounted for 10% of lymphoma prevalence in the world with high distribution in Asia and NK- cell lymphoma is diagnosed not more than 1%. B cell lymphoma has the commonest subtypes, including; Diffuse Large B-Cell Lymphoma (DLBCL), folecular lymphoma, Burkitt lymphoma, marginal zone lymphoma (MZL) and mantle cell lymphoma. Among this DLBCL and T- cell lymphoma are the most widespread NHLs among adult Ethiopians(1, 2).

Although the cause of NHL is still idiopathic, certain risk factors like infections including HIV/AIDS, Hepatitis B virus, Epstein-Barr virus (EBV), Hepatitis C virus (HCV) and Helicobacter pylori have been identified (1). Iatrogenic immunosuppressant and autoimmune diseases such as chronic inflammatory diseases, lymphomagenesis, Sjogren's syndrome, systemic lupus erythematosus and rheumatoid arthritis increased the chance of NHL(1).

Non- Hodgkin's Lymphoma accounts for 2.8% of all cancer cases and 2.6% of all cancer morbidity. It is the 8^{th} and the 10^{th} most commonly diagnosed malignancy among men and women respectively (3). The incidence and mortality of NHL is higher in men [worldwide age-standardized rate (ASR) 7.8 and 4.3/100 000] than women (ASR 5.6 and 2.8/100 000) respectively (3). In Ethiopia, hematological malignancies are the 12^{th} most common cancers, as they accounted for 9% of all cancer visits; of which lymphoma ranked as 5^{th} and 7^{th}

commonest malignancy among male and females in TASH (Tikur Anbessa Specialized Hospital) correspondingly(3, 4).

1.2. Statement of the Problem

Cancer is the second leading cause of death globally (5). About 1 in 6 deaths on the world are due to cancer from which 70% of deaths occur in low- and middle-income countries (6). In Ethiopia, most Hematological Malignancies are among top thirty cancers in the country; of these Non Hodgkin's lymphoma, ranked as 5th most prevalent and 10th deadliest cancer (7). In 2015, it was the second leading malignancy among adult men, (fifteen years and older), and pediatric (age less than fifteen) with estimated new case of 2305 (10.6%) and 510 (14%) respectively. The prevalence increased with age, making elder adults (sixty five and above years old) the most vulnerable groups. In western part of the country it is established that from total of 83 cases of lymphoma, non Hodgkin's lymphoma accounted for 61(73.5%); the predominant sub types were high grade lymphoma (41%) and low grade lymphoma (32.8%) followed by Burkitt's lymphoma(8, 9).

As treatments of NHL enhanced from day to day the prognosis, survival and quality of life also improved considerably in developed parts of the world. Though some NHL have good prognosis, limited access to diagnosis, delayed presentation; advanced disease, co-morbidities and underlying malnutrition further aggravate treatment complication (10) leading to poor prognosis in under developed countries. As most developing countries these malignancies are still peaked up in Ethiopia, both in incidence and mortality (7). In addition to this, late presentation also reduced the chance of cure as 90% of cancer patients in TASH presented at stage III and VI (11) . Nevertheless, in many cases the treatment goal isn't clearly stated either they are palliative or curative.

Predictors of NHL were studied and documented on different parts of the world on many different books and scientific journals. Aside from genetic studies, which is costly and not viable to be applied in developing countries like Ethiopia, numerous literatures from different countries stated practically applicable predictors, including socio demographic factors, age, sepsis, reduced immunity and patho - clinical factors; particularly hematological measurements like Complete Blood Counts (CBC). These predictors were shown to substantially predict the outcome of several NHL patients, who were on diverse therapeutic regimens (12-15).

Even though, there are various evidences that highlight; patients with cancer can gain much from palliative care including reductions in symptom burden, improvements in quality-of-life, mood, survival, and caregiver burnout; aggressive treatment is usually provided to patients with incurable NHL, instead of palliative and end of life care. This is due to uncertain trajectories, indistinct transitions and difficulties in predicting prognosis. Even if NHL is identified as incurable, many clinicians remain reluctant to withdraw aggressive treatment and refer patients to palliative care. This could also be due to lack of experience by many hematologist-oncologists about referring to palliative care (16). These have lead to difficulties for determining the appropriate time to initiate discussions about end-of life care. As a result numerous NHL patients still suffer from symptom burden and complication from different types of treatments, in spite of significant improvements in the medical world (4, 17).

Generally, patients with Hematological Malignancies have minimal access to palliative care and end of life services than patients with solid tumors as they are usually hospitalized during the last month of their life and frequently die in the hospital receiving aggressive anti cancer treatments. These commonly causes, overtreatment, unnecessary stress and reduced quality of life, also often considered as a reflection of poor end-of-life care (18); its effect is considerably high in set ups like TASH. Thus accurate risk stratification is essential for successful treatment. So, the outcome of patients with NHL in different setting should be identified; as advance planning and better communication between clinicians enhances quality of life (16); so nurses should step up to make a difference on survival and quality of life of these patients by facilitating communication and acting as patient advocate. However, to the best of the PI search on Pub Med, Medline and Google Scholar there is little to no documentation on the outcome and its predictors among NHL patients in Ethiopia. So the present study primarily aimed to assess outcome of patients with non Hodgkin's Lymphoma and its predictors at TASH.

1.3. Significance of the Study

Prognostic factors in cancer patients offer more information about possible clinical outcomes, which helps clinicians to stratify patients in to different risk groups. As NHLs are diverse groups of cancers, their treatment and clinical management decisions are often challenging, thus the availability of feasible and practical prognostic markers is vital in order to design treatment plans and discus possibilities with patients as well as care givers.

Nurses' play a vital role to the improvement of patients' quality of life and overall survival by offering quality care. Cancer patients especially those suffering from incurable diseases, usually deal with intricate physiological, psychosocial and spiritual needs; so nurses have to provide palliative care to these vulnerable groups. In order to give appropriate holistic care; patients' should be stratified according to the outcome of their illness; so that palliative and/ or end of life care would be initiated as soon as possible. Therefore, identifying predictors of NHL in once working area will be helpful for care providers to have a better understanding about the patients' including their needs in order to offer evidence based care. Additionally, determining the outcome and its predictors' among NHL patients enhances the ability of nurses to be a good patient advocate, communicator and educator.

Furthermore, it will assist concerned bodies to give attention for predictors and prognosis indicators of NHL and initiate appropriate intervention, to improve survival rate of cancer patients as well as their quality of life.

Thus, this study is believed to provide relevant information about outcome, and outcome predictive factors among patients with Non Hodgkin's Lymphoma, at Tikur Anbessa Specialized Hospital. Additionally, it will also serve as a base line data for further research in the future.

2. LITERATURE REVIEW

Non- Hodgkin's Lymphoma is diverse group of disorders having more than thirty sub types, among this commonest sub types of NHL are diffuse large B cell, follicular, Burkkit and T cell lymphoma. There is a large variation in the geographical distribution of NHL sub types as studies conducted in different parts of world have reported substantial variation on the overall incidence of NHL and its specific subtypes, although various studies used different NHL classification systems. Compared to the developed world, developing countries including Ethiopia had a significantly a lower frequency of B-cell lymphoma (90.7%) and higher frequency of T (9.3%), - and natural killer-cell lymphoma (86.6% and 13.4%) respectively (2, 19-21).

2.1. Outcome of Non-Hodgkin's Lymphoma

The outcomes of hematological malignancies' vary in different parts of the world. Depending on socio demographic, patient related factors, disease related factors and treatment related factors. Death from hematological malignancies is usually related to organ failure, hemorrhage and majorly infection. The same is true in TASH as 43% of patients with HM died as a result of infection (22). Yet, the five-year cancer-specific survival increased dramatically over time for DLBCL (from 37% to 66%) and follicular lymphoma (-69%-82%) (23). The overall five year survival of patients in USA from NHL has reached 71%, due to improvements in medicine (24).

Lifelong follow up is usually recommended for all survivors of cancer based on risk stratification; Yet lost follow up is higher in developing countries related to age, prolonged travel time to treatment facility (hazard ratio=3.1), for 2-3 hour travel and for >5 hour travel (25).

2.2. Predictors of Outcome

2.2.1 Socio demographic parameters

Although the overall five year survival of patients with DLBCL was significantly enhanced, various non-biological factors still continued to hamper the survival of NHL patient's in spite of medical miracles. The incidence of NHL usually rises on the 5^{th} to 7^{th} decade of life and it is usually associated with poorer overall (OS) five year survival (15). According to, a retrospective, multicenter, registry-based study, conducted in France; age 73-80years, 81-99 years, sex, marital status, co morbidity and registry area, were found to be independent predictors (26).

2.2.2. Patient related factors

2.2.2.1. Hematologic parameters

Retrospective study conducted in china, studied newly diagnosed Diffuse Large B-Cell Lymphoma (DLBCL) patients treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy; and the prognostic impact of Lymphocyte-to-Monocyte Ratio (LMR)<2.6 at diagnosis on the survival of DLBCL patients was determined as an independent prognostic factor for overall survival and progression free survival (PFS), when adjusted with other strong predictive parameters such as age >60, Ann Arbor stage (III and IV), ECOG PS ≥2, serum LDH level >245 U/L, Extranodal sites, AMC (absolute Monocyte Count) $\geq 0.62610^9$/L, ALC (absolute lymphocyte count) $\leq 1.10610^9$/L (27). Additionally, LMR<2.6 remained as independent predictor of poor prognosis for both overall and progress free survival when adjusted for variables of IPI (international prognostic index) score (27) .

Another retrospective cohort study conducted in china on other type of NHL, which is Extra nodal Natural Killer/T-cell Lymphoma, Nasal Type (ENKTL), with LMR cutoff point of 2 also determined, that low LMR at diagnosis had substantial association with PFS, when adjusted to age and treatment stratagem; and overall survival when adjusted to age, elevated LDH, local tumor invasiveness and treatment stratagem Furthermore, lower LMR determined treatment modality, as patients with low LMR received only chemotherapy; where

chemotherapy alone, radiotherapy alone and both chemotherapy and radiotherapy were the primary treatment modalities. The treatment regimens of chemotherapy in the initial treatment included; CHOP, CHOPL (CHOP and L-asparaginase), GELOX (gemcitabine, oxaliplatin and L-asparaginase), and EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone) (28-30).

A study analyzed newly diagnosed Taiwanese diffuse large B-cell lymphoma patients who started treatment by (R)-CHOP-like regimens retrospectively, identified that the ALC/AMC is more reliable than the NLR and LMR based on the akaike information criterion (AIC) analysis with scores of 372.574, 388.773 and 387.62 respectively. The predicted 5-year PFS of patients was 64.2%, and the 5-year OS was 71.4%, when adjusted to advanced age, advanced stage, reduced hemoglobin count, higher ECOG performance status score, ALC and AMC (28, 31).

Institutional retrospective study conducted in Korea estimated the outcome and prognostic factors by reviewing medical records for clinical and laboratory data during diagnosis of patients with MZL and treated with rtuximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) regimen. The most discriminative ROC curves for Platelet – lymphocyte – ratio (PLR) was 95, with (sensitivity 82.3% and specificity 55.6%; AUC values 0.623. Patients having PLR >95 had better overall and progress free five year survival (31). An observational retrospective, multi-cohort study conducted in Italy, studied the outcome of HIV related NHLs, and affirmed that, risk of mortality was 3.11 and 2.34 times higher among patients with LMR<2.11, NLR>4.35 and PLR<150 respectively (26).

2.2.2.1. Performance and Lactaye Dehydrogenous related Factors

Even if palliative chemotherapy alleviates symptoms and used to improve quality of life (QOL) for patients with advanced cancer, its use did not improve QOL for patients with moderate or poor performance status. Aggressive chemotherapy for patients with incurable cancer is demonstrated to worsen QOL, still for patients with good performance status. As ECOG 1 associated with decreases QOL (32). Although, ECOG still recorded on different articles as both dependant and independent predictor of OS and PFS among patients with different sub types of NHL, CCI predicted PFS more precisely compared to ECOG (15, 31).

Elevated serum lactate dehydrogenous is also found to be an independent poor prognostic indicator (30, 31, 33)

2.2.3 Disease Related Factors

About one third of NHL patients, particularly patients with DLBCL, develops relapsed disease; in spite of enhanced survival. Type of NHL is also listed as one prognostic indicator of survival from malignancy. Generally, People with B-cell lymphomas often have a superior chance of prognosis than those with T-cell lymphomas; additionally Indolent NHL types also have better chance of survival compared to aggressive ones, with median survival duration of 20 years. Of the 2 most common types of B-cell lymphoma, follicular lymphoma usually had an enhanced prognosis than DLBCL. It compresses 70% of indolent lymphoma and 20% of all NHL in USA and Europe with good prognosis ranging from 8 to 15 year OS, in spite of stage; while DLBCL which is an aggressive type, has 96% and 30% chance to five year OS for low risk and high risk patients respectively. "Anaplastic large cell lymphoma and cutaneous T-cell lymphoma are 2 subtypes of T-cell lymphoma that have a fairly good prognosis"(34).

Patients having co morbidities usually had lower rate of complete remission and 4.12 times higher hazard of mortality as a result of treatment related toxicity and frequent dose reductions. A retrospective chart assessment study carried out in China, by sampling 56 newly diagnosed elder Peripheral T cell lymphoma patients, discerned that 50% of the population had co morbidity, lead by debates mellitus and cardiovascular disease. ECOG (2-4) score and co morbidity (Charlson Comorbidity Index (CCI) ≥2) are proved to correlate to each other, in addition to significant relation with overall survival (35).

A retrospective chart review study was conducted in USA, by sampling 176 DLBCL patients and found CCI as predictor of both OS and PFS. The prevalence of co morbidity among aggressive NHL patients was frequently age dependent, as co morbidity was observed in 80% and 45%, of NHL patients, age >60 and 40-60 years correspondingly. Severity of CCI score is an additional determinant of prognosis, as the overall five year survival of patients with CCI lower score (0-2) is 70%, while patients with high CCI (≥3) had the overall five year survival of 51% with a median survival duration of 136 and 50 months respectively(15). Infection was

common among patients with CCI score ≥3, and it increased risk of mortality by 3.27 folds (36).

Although about 50% of patients with DLBCL cured after initial treatment, 20-30% of patients developed relapse within two years of completion of initial treatment. Prognosis significantly varied with stage, type, stage, age, performance status, and lactate dehydrogenase levels(37).

2.4. Conceptual Frame Work

The conceptual frame work is prepared by principal investigator based on literature review (13, 15, 26-29, 33, 35-48). Socio demographic factors, patient related factors, disease related factors and treatment related factors were significantly associated with the outcome of hematological malignancies.

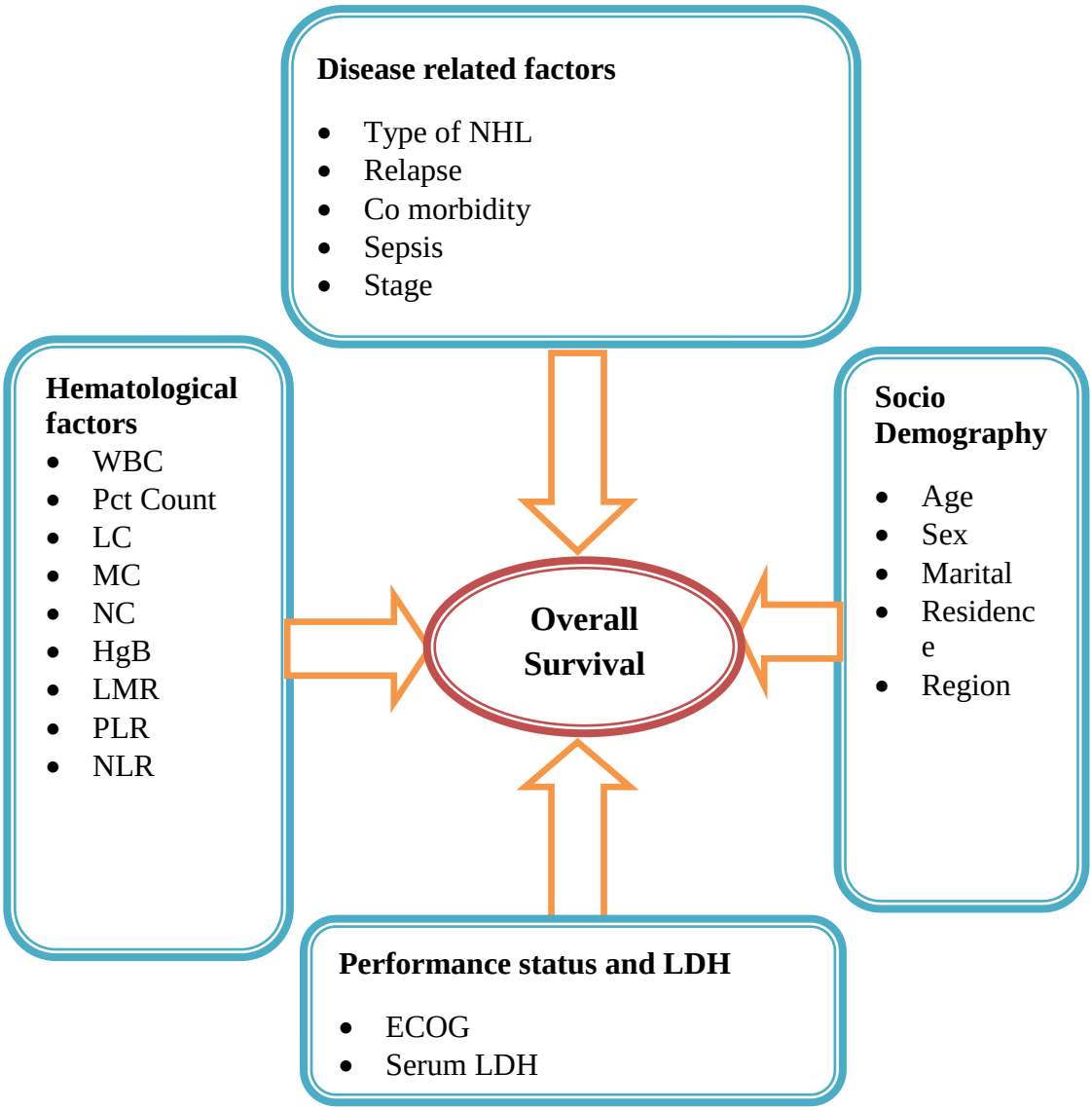

Figure 1: Conceptual frame work based on literature review (14, 16, 27-30, 34-48) Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia; 2019

3. OBJECTIVE OF THE STUDY

3.1. General Objective

- To assess Outcome of patients with non Hodgkin's lymphoma and its predictors, at Tikur Anbessa Specialized Hospital: A retrospective chart review; Addis Ababa, Ethiopia, 2019

3.2. Specific Objectives

- To assess the outcome of Non Hodgkin's Lymphoma patients admitted at Tikur Anbessa Specialized Hospital: A Retrospective Chart Review; Addis Ababa, Ethiopia, 2019.
- To identify outcome predictors' among Non Hodgkin's Lymphoma patients admitted at Tikur Anbessa Specialized Hospital: A Retrospective Chart Review; Addis Ababa, Ethiopia, 2019.

4. METHODS AND MATERIALS

4.1. Study Area and Period

4.1.2. Study Area

Addis Ababa is the largest city in the country. It headquarters different national and continental organizations. It is estimated that the city has 2,739,551 inhabitants in 2007 (49).

TASH is the largest referral hospital and the only hematology center in the country. This hospital offers diagnosis and treatment for approximately 370,000-400,000 per year. The provided service includes; Anti neoplastic drugs, surgery and radiotherapy for non Hodgkin's lymphoma and other malignancies with a limited material and personnel rescores. Hematology department offers services for nearly 15,800 blood cancer patients per annum (22). So, this study took place at Adult Hematological units of TASH and Amistegna.

4.1.2. Study period

The study had been conducted at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia; from February to April 2019.

4.2. Study Design

Institutional based retrospective study had been conducted at Tikur Anbessa Specialized Hospital: Addis Ababa; Ethiopia, 2019.

4.3. Population

4.3.1 Source population: All patients with non Hodgkin's lymphoma in Ethiopia

4.3.2 Study Population - All patients with non Hodgkin's lymphoma who were admitted at TASH

4.3.3 Study Unit - All patients who started treatment for non Hodgkin's lymphoma at TASH, from January 2014 to January 2016.

4.4. Inclusion and Exclusion Criteria

4.4.1. Inclusion Criteria: Patients admitted at TASH with diagnoses of NHL and Patients on CHOP and (R)-CHOP regimen of NHL therapy

4.4.2. Exclusion Criteria: Charts with incomplete information about independent variables.

4.5. Sampling

According to TASH medical and Hematological unit medical registration report, the total number of the Population is less than 200, which is lower than calculated sample size; so population census is used. That is all charts of patients with non Hodgkin lymphoma diagnosis; from January 2014 to January 2016 in TASH are sampled.

4.6. Operational Definition

Non Hodgkin's Lymphoma (NHL): cancers which originate from lymphatic and immune systems, including lymphocytes and lymph nodes (1); except Hodgkin's Lymphoma.

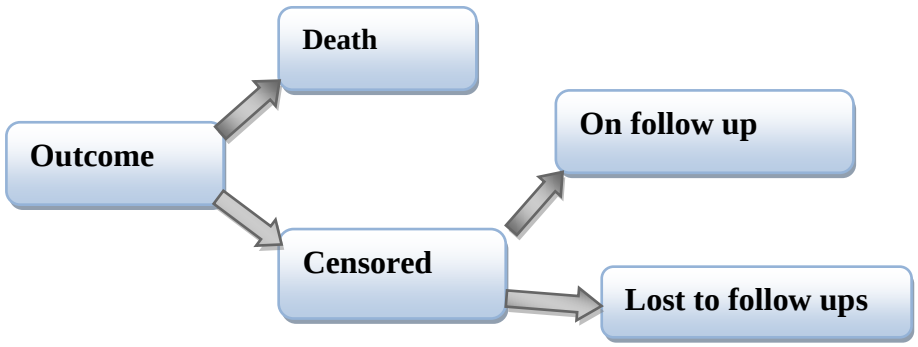

Figure 2: outcome of Non Hodgkin's Lymphoma, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019

Outcome: Death, on follow ups or lost to follows ups

Death: is the event

On follow up: NHL patients seeking treatment during data collection; measured from the date of diagnosis to the date of last follow-up

Lost to follow-ups - patients who quite treatment against medical advice; measured from the date of diagnosis to the last treatment discontinued date

OS (Overall survival) – the time between the first day of diagnosis and the date of death from any cause (50)

Predictor: factors having statistical significance with event (51)

Adult: Age ≥15 years(52)

CHOP-treatment with combination of Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

(R)-CHOP-treatment with combination of Rituximab plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

4.7. Definition of Variables

Co morbidity: Charlson co morbidity index (CCI) was used to calculate severity of co morbidity according to the 19 conditions described originally, except for "lymphoma". CCI <3 and ≥3 are classified as low and high sever co morbidity.

Table 1: Charlson Co morbidity Index for Non Hodgkin's Lymphoma at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, 2019

Condition	Variable Name	Points	Notes
Myocardial infarction	MI	1	
Congestive Heart failure	CHF	1	
Peripheral vascular disease or bypass	PVD	1	
Cerebrovascular disease or transit ischemic disease	CVA	1	CVA Only

Hemiplegia	PLEGIA	2	If hemiplegia, don't count CVA separately
Pulmonary diseases/ asthma	COPD		
Diabetes	DM		DM only
Diabetes with end organ damage	DMENDORGAN	2	If end organ damage do not count DM separately
Renal disease	RENAL	2	
Mild liver disease	MILDLIVER	2	
Severe liver disease	SEVERLIVER	3	
Gastric or peptic ulcer	ULCER	1	
Cancer (lymphoma, leukemia, solid tumor)	CANCER	2	Non metastatic cancer only
Metastatic solid tumor	METASTASES	6	If metastatic, don't count cancer separately
Dementia or Alzheimer's	DEMENTIA	1	
Rheumatic or connective tissue disease	RHEUMATIC	1	
HIV or AIDS	HIV	6	
Hypertension	HBP	1	
Skin Ulcers/ cellulites'	SKIN ULCER	2	
Depression	DEPRESSION	1	
Warfarin	WARFARIN	1	

Source: (44)

Relapse: recurrence of non Hodgkin's lymphoma after complete remission (no of evidence of lymphoma)(37).

Staging

Table 2: staging of Non Hodgkin's Lymphoma at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, 2019

Stage		Involvement	Extra nodal status
Limited	**I**	One node or a group of adjacent nodes	Single extra nodal lesions without nodal involvement
	II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extra nodal involvement
II bulky		II as above with "bulky" disease	Not applicable
Advanced	**III**	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen Involvement	Not applicable
	IV	Additional noncontiguous extra lymphatic involvement	Not applicable

Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

Source: (53)

Performance status (ECOG): assess the influence of disease and treatment on patients' daily living (54).

Table 3: Eastern Cooperative Oncology Group (ECOG) Performance Status, Tikur Anbessa Specialized Hospital, Addis Ababa; Ethiopia, 2019

Grade	ECOG
0	Fully active, able to carry all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of alight or secondary nature, e.g. light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of working hours
3	Capable of only limited self care, confined to bed or chair more than 50% of working hours

4	Completely disabled cannot carry on any self care. Totally confined to bed or chair
5	Dead

Source: (54)

White Blood Cell Count (WBC) - in adults range from 3,500 to 11,000 (cell/mm^3); while >50,000(cell/mm^3) is considered as leukocytosis (55).

Platelet count-normal range is 250,000-450,000(cell/mm^3);, but <150,000(cell/mm^3) is considered as thrombocytopenia (56)

Hemoglobin count-normal range is 12.8–19.0 g/L, (57) while <12 g/dL is generally considered as anemia(56)

Neutrophil count-the normal range is from 2000-7000(cell/mm^3); but ≥7,500 (cell/mm^3) is considered as Neutropenia(56)

Monocyte count –the normal range of monocyte count is 200-1000 cell/mm^3, yet>630(cell/mm^3) is considered as monocytemia(56).

Lactate Dehydrogenious (LDH) -although the normal range varies widely, >245 U/L is considered as elevated(42)

Lymphocyte count: the normal range is 1000-3000(cell/mm^3); but ≤1000 is considered as Lymphopenia(14)

4.8. Variables

4.8.1. Dependent Variable

Overall survival

4.8.2. Independent Variables

4.8.2.1. Socio demographic variables

Age

Sex

Marital status

Region

Place of Residence

4.8.2.1. Disease related factors

Type of NHL

Relapse

Co morbidity

Stage of the malignancy

Sepsis

4.8.2. 3. Patient related factors

4.8.2.3.1. Hematological factors

White blood cell count

Monocyte count

Lymphocyte count

Monocyte count

Hemoglobin

Platelet count

LMR

NLR

PLR

4.8.2.3.2 Performance related factors

Performance status (ECOG)

LDH

4.9. Data Collection and Data Analysis Plan

4.9.1 Data collection

The data were gathered by using structured checklist, for recording information extracted from patient charts. The tool was prepared by PI depending on literatures, and it was validated by one Hematologist and two internal Medicine Residents. It was prepared and administered in English. The data collection tool contains both multiple choice and open ended questions, which mainly focused on outcome and its predictors among patients with non Hodgkin's

Lymphoma. The tool has four parts. The first part asks about socio demographic status; while the second disease related factors, third patient related factors and fourth the part focused on performance status and LDH. Data were gathered by four trained BSc. Nurses, who work at hematology unit; and it, was supervised by two MSc. Clinical Oncology nurses. The training was given for data collectors by Master of Public Health (MPH) and principal investigator. In order to have a common understanding about the data collection tools, the research proposal and the data collection tools were also presented to data supervisors by PI.

4.9.2. Data quality control

At the end of each day the questionnaire was checked for completeness of each question, and carefully entered into the Epi data version 3.1 throughout the study. The reliability of the instrument was identified by calculating Cronbach's alpha using SPSS version 20.

4.9.3. Data analysis

Data were coded, in order to avoid missing and entered in to Epi data version 3.1 and exported to SPSS version 20.0 for analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values of the LMR, NLR, and PLR, values with the maximum joint sensitivity and specificity were selected. Frequency distributions and proportions were analyzed. OS (Overall survival) outcomes were analyzed using Kaplan–Meier Log-rank model for estimation of survival duration in months. Cox proportional hazards regression models was performed with 95% CI to calculate hazard ratio in order to identify dependent and independent predictors. Univariate Cox regression was done before multivariate analysis as a result parameters ($P<0.2$) are considered as fitted variables for multivariate analysis. On multivariate analysis variables with ($P<0.05$) are considered as independent predictors of overall survival.

4.10. Ethical Consideration

Ethical clearance and approval for the study was obtained from the ethical committee of Addis Ababa University, college of health sciences, school of nursing and midwifery. Permission to conduct the study and consent was also obtained from Tikur Anbessa Specialized Hospital and patient or relative, respectively. Privacy, confidentiality and

anonymity were guarded. Scientific objectivity of the study was maintained with honesty and impartiality.

4.11. Result Dissemination Plan

The result will be disseminated by submission of publication and presentation to Addis Ababa University School of nursing and midwifery, Tikur Anbessa Specialized Hospital. Additionally the thesis will be published on reputable and peer reviewed journals.

4.12. Limitation of the study

On this study data were extracted from secondary sources, retrospectively. This may increase recorder biases and it hinders the full accessibility of some variables. Because of reduced sample size, the variation of outcome and associated predictors in different sub types of Non Hodgkin's Lymphoma were not analysed. Since, TASH is the only hematological center in the country this study was conducted there. Thus, the external validity might be limited to a single institution

5. RESULTS

A total of 123 adult patients were diagnosed with NHL from January 2014 to January 2016; yet, due to incompleteness 52 charts where excluded, as a result 71adult patient charts were reviewed on this study. The socio demographic, outcome, disease, patient and performance related factors all have been summarized in tables.

5.1. Socio Demography characteristics

The median age of study participants at diagnosis was 56 years (SD±17.46), and ranges from 16 to 78. More than half of them were males 43(60.6%). Most of them were married (55) 77.5. About half of the patients were from Oromiya region 33(46.5%), while 41(57.8%) of them were urban residents.

Table 4: Distributions of socio demographic characteristics among study subject at Tikur Anbessa Specialized Hospital Addis Ababa, Ethiopia, from January 2014 -2016, N=71

Parameter		**Death**		**Censored**		**Total**	
		N	**%**	**N**	**%**	**N**	**%**
Age (years)	15- 60	20	46.5	19	67.9	39	55
	≥60	23	53.5	9	32.1	32	45
Sex	Male	27	62.8	16	57.2	43	60.6
	Female	16	37.2	12	42.8	28	39.4
Marital status	Single	7	16.3	6	21.4	13	18.3
	Married	34	79	21	75	55	77.5
	Others*	2	4.6	1	3.5	3	4.2
Region	Oromiya	22	51.2	11	39.3	33	46.5
	Amhara	11	25.6	12	42.9	23	32.4
	SNNPR	10	23.3	3	10.7	13	18.3
	Others**	-		2	7	2	2.8
Residence	Urban	26	60.5	15	53.6	41	57.8
	Rural	17	39.5	13	46.4	30	42.2

Others*- widowed and divorced; others**- AA and Tigray

5.2. Outcome of NHL

The mean duration of follow ups for died patients, on follow ups and lost to follow ups patients was 17.3, 41.7 and 21.9 months respectively.

Table 5: Outcome of NHL among study subject, at Tikur Anbessa Specialized Hospital Addis Ababa, Ethiopia, from January 2014 -2016, N=71

Parameter		Death		Censored		Total	
		N	%	N	%	N	%
Outcome	Death	43	100	-	-	43	60.6
	On follow up	-	-	19	67.9	19	26.8
	Lost follow up	-	-	9	32.1	9	12.7
Follow up duration in Months	<36	43	100	15	53.6	58	81.7
	≥36	-	-	13	46.4	13	18.3

5.3. Disease related factors

Large diffuse B cell lymphoma was quite common among died patients 24(55.8%), followed by T cell 13(30.2%); yet T cell lymphoma shown to be by far the commonest among patients on follow ups. As NHL is frequent among immune compromised patients, HIV is the most widespread co morbidity accounting for about 14(31%) of all co morbidity.

Table 6: Disease Related Factors among Study Participants, at Tikur Anbessa Specialized Hospital Addis Ababa, Ethiopia, from January 2014 -2016, N=71

Parameter		Death		Censored		Total	
		N	%	N	%	N	%
Type of NHL	Large diffuse B cell	24	55.8	15	55.6	39	55
	T cell lymphoma	13	30.2	9	32.1	22	31
	Burkkits lymphoma	4	9.3	3	10.7	7	10

	Other*	2	4.7	1	3.6	3	4
Relapse	Yes	20	46.5	2	7.1	22	31
	No	23	53.5	26	92.9	49	69
CCI	≥3	32	74.4	12	43	44	62
	<3	11	25.6	16	57	27	38
Stage	≥2	35	81.4	5	12.9	40	56.3
	<2	8	18.6	23	82.1	31	43.7
Sepsis	Yes	29	67.5	17	60.7	46	64.8
	No	14	32.5	11	39.3	25	35.2

Other*- Follicular Lymphoma; CCI- Charlson Co- morbidity Index

5.4. Patient related factors

The cut-off points of LMR, NLR and PLR for survival outcomes were selected by the ROC analysis. The most discriminative cut-off value of PLR = 144, with an area under the curve (AUC) value of 0.611 [95% CI, (0.866-1)], NLR=2.8; [AUC= 0.651, 95%CI, (0.5-0.8)] and LMR = 3.1; [AUC = 0.845, CI 95%, (0.469-0.754)]. Based on these results, LMR ≥ 3.1, NLR ≤2.8 and PLR 144 were selected optimal cut- off points. (Summarized on finger 3, 4 and 5)

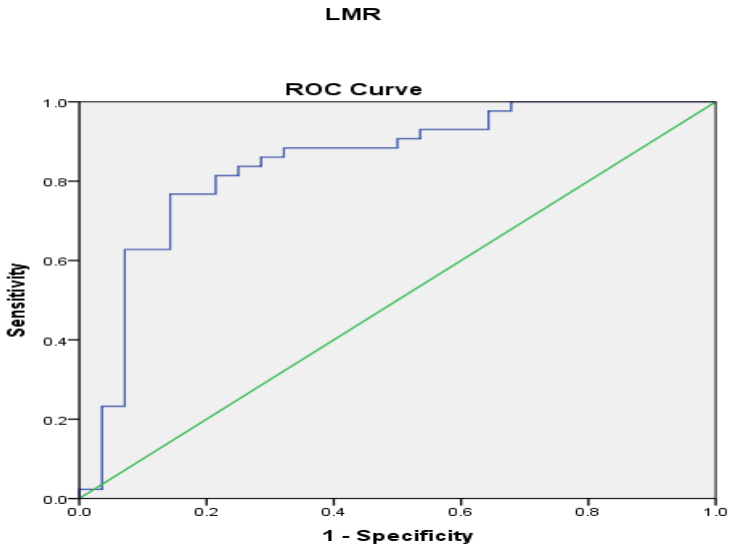

Figure 3: A Receiver Operating Characteristic (ROC) Curves Analysis for LMR during Diagnosis, Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016, N=71

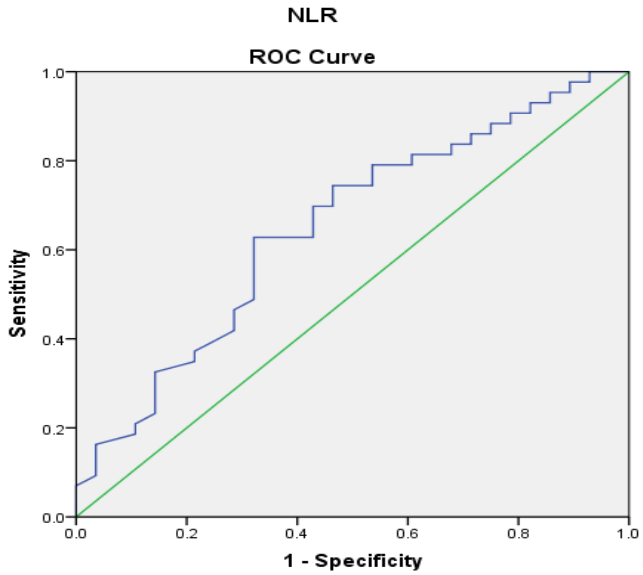

Figure 4: Receiver Operating Characteristic (ROC) Curves Analysis for NLR during Diagnosis, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

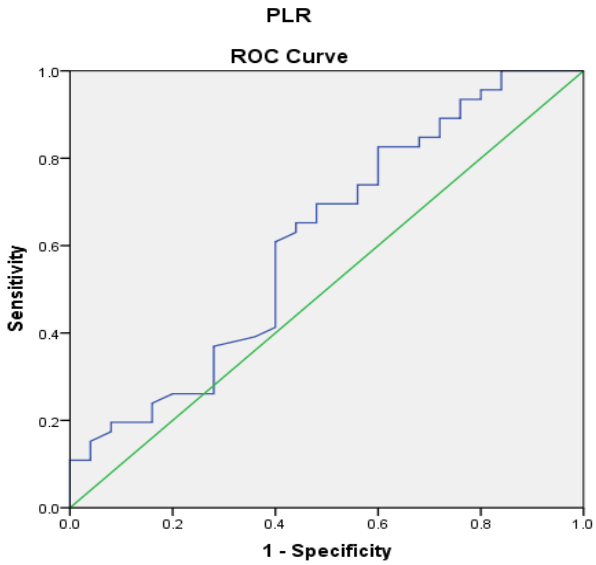

Figure 5: Receiver Operating Characteristic (ROC) Curves Analysis for PLR during Diagnosis, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

The platelets count (PC), Neutrophil count (NC), Monocyte count (MC) and Lymphocyte count (LC) were derived from pre-treatment (Complete Blood Counts) CBC. The median, PC NC, MC, and LC of all patients at diagnosis were 167,500, 7620, 766.7, 1253.2 respectively. (Shown on table 7 below)

Table 7: Hematologic Parameters of Study Participants, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

Parameter		**Death**		**Censored**		**Total**	
		N	**%**	**N**	**%**	**N**	**%**
WBC (cell/mm^3)	≥50,000	15	34.9	12	42.9	27	38
	<50,000	28	65.1	16	57.1	44	62
Monocyte count (cell/mm^3)	≥630	31	72	3	10.7	37	52
	<630	12	28	25	89.3	34	48
Lymphocyte	<1000	30	69.8	4	14.3	34	47.9
count(cell/mm^3)	≥1000	13	30.2	24	85.7	37	52.1
Neutrophil count	≥7500	41	95.3	10	35.7	51	72
(cell/mm^3)	<7500	2	4.7	18	64.3	20	28
Platelet count (cell/mm^3)	<150000	16	37.2	9	32.1	35	49.3
	≥150000	27	62.8	19	67.9	36	50.7
LMR	<3.1	27	62.8	2	7.1	29	40.8
	≥3.1	16	37.2	26	92.9	42	59.1
NLR	<2.8	17	39.5	10	35.7	27	38
	≥2.8	26	0.6	18	64.3	44	62
PLR	≥144	33	76.7	6	21.4	39	55
	<144	10	23.2	22	78.6	32	45
Hgb count (gm/dL)	<12	29	67	17	60.7	46	64.8
	≥12	14	32.5	11	39.3	25	35.2

WBC- White Blood Count; LMR- Lymphocyte Monocyte Ratio; NLR- Neutrophil Lymphocyte Ratio; PLR- Platelet Lymphocyte Ratio

5.5 Eastern Cooperative Oncology Group and Lactate Dehydrogenous

Died NHL patients showed elevated LDH and higher ECOG score than censored patients 33(76.8 %) and 33 (76.8), respectively.

Table 8: Eastern Cooperative Oncology Group and Lactate Dehydrogenous among Study Participants, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

Parameter		**Death**		**Censored**		**Total**	
		N	%	N	%	N	%
ECOG	≥2	33	76.8	18	64.3	51	71.9
PS	<2	10	23.2	10	35.7	20	28.1
LDH	≥245U/L	33	76.8	19	67.9	52	73.2
	<245 U/L	10	23.2	9	32.1	19	26.8

ECOG PS- Eastern Oncology Group Performance Status; LDH- Lactate De Hydrogenous

5.6. Incidence and overall survival status of NHL patients

The anticipated overall survival of NHL patients for 12, 24, 36, 48 and 60 months were 83.1%, 70%, 58%, 42.4% and 32.1% correspondingly**;** with the median survival of 27 months, 95% CI, [21.98-32.01] (summarized on Figure 6).Total observed deaths throughout the study were 43(60.56%) making the total amount of observed person to time 144.4 person-years, with an incidence rate of 34 deaths per 100 person-years. Mortality was substantially increased from 30 months on, as illustrated on the figure 6 below.

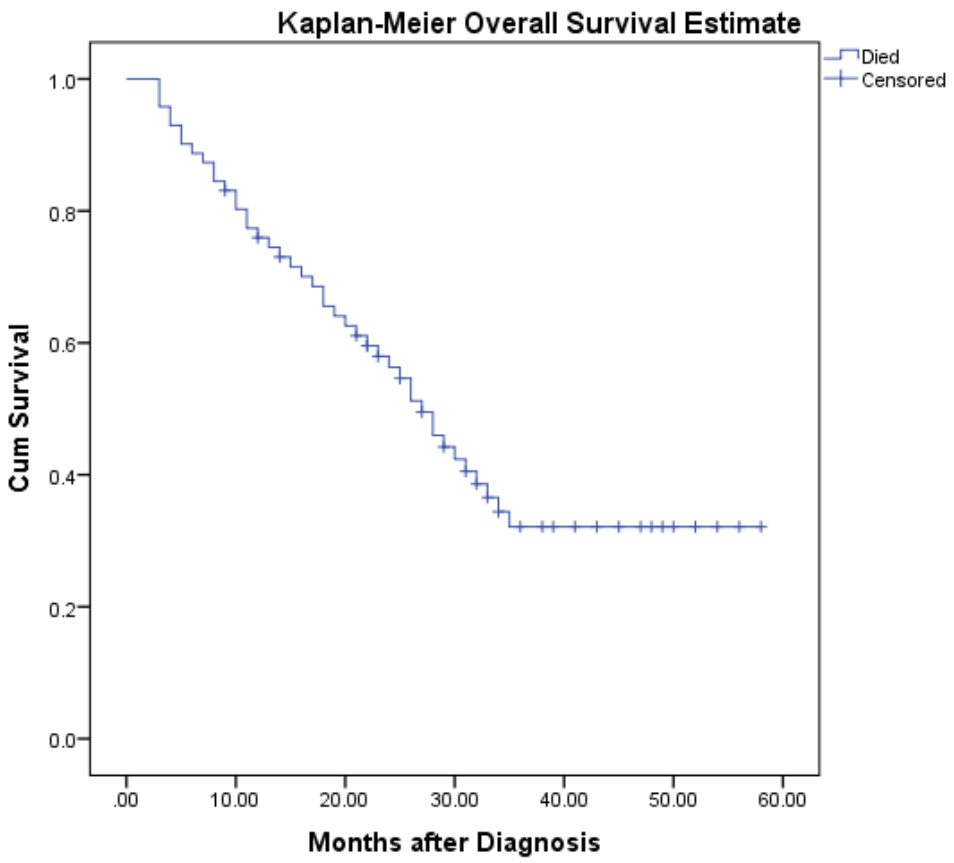

Figure 6: Kaplan–Meier curves for 5-year overall survival of NHL, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

5.7 Survival function among different groups of NHL patients

Log-rank test was performed to compare the survival distribution among died and censored patients, based on different study variables. As a result the presence of substantial variation in survival duration among different variables and fairness of survival curves on this study had been identified and summarized on table 9 below.

Table 9: Loge rank for 5-year overall survival of NHL, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

Parameter		Log rank	P- value	Median survival time in months [95%CI]	Overall 5 year survival (%)
Stage	≥2	23.7	0.000	19[14.2-23.8]	7
	<2			31[26.2-36.1]	70
Relapse	Yes	39	0.00	10[6.6-13.4]	9.1
	No			33[27.6-38.4]	42.9
CCI	≥3	14.5	0.000	23[16-30]	00
	<3			36[31.3-44.6]	61.9
LMR	≤3.1	23	0.00	16[2-30]	5.2
	>3.1			27[22-32]	54.4
NLR	≥2.8	3.54	0.045	17[6.3-27.7]	26.9
	<2.8			28 [22.2-33.8]	35.6
PLR	<144	23.4	0.00	16[10.5-21.5]	9.7
	≥144			31[26.2-36.1]	55.3
LDH	≥245	9.48	0.002	22[14.8-29.12]	19
	<245			32[26.2-36.1]	52.6

The anticipated overall survival of NHL patients with relapse for 12 and 20months were 45.5% and 9.1% respectively as shown on Figure 7 below.

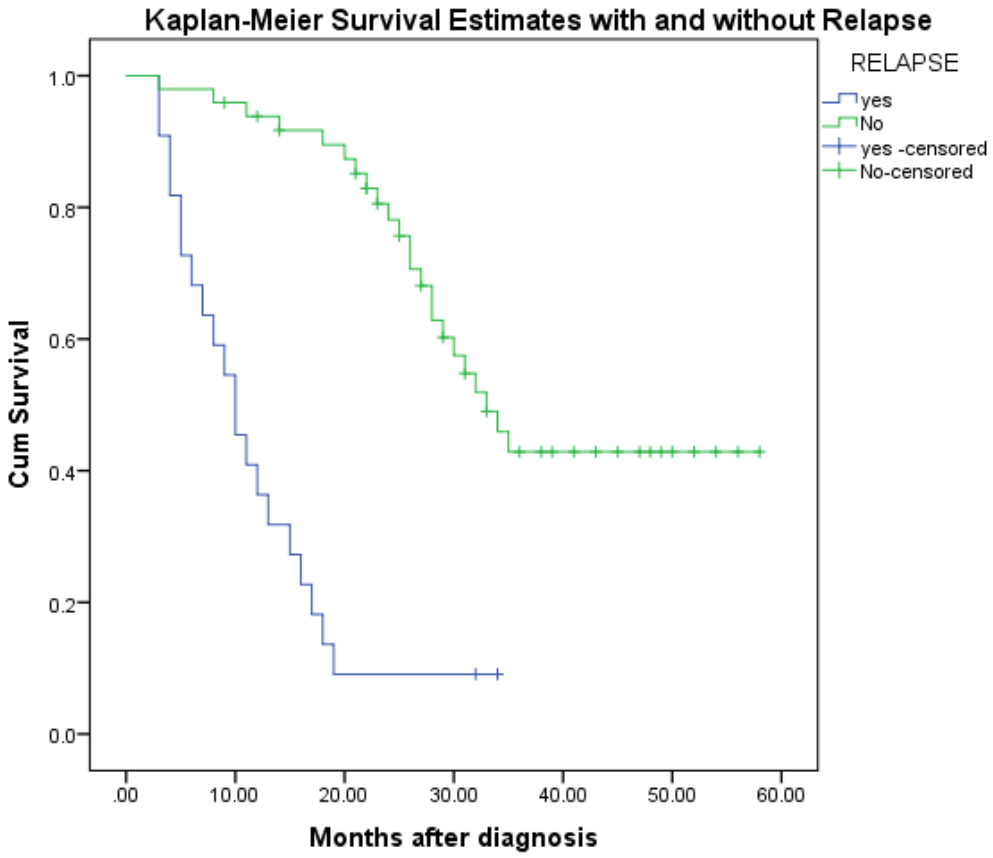

Figure 7: Kaplan–Meier curves for 5-year overall survival of NHL, regarding Relapse, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

The anticipated overall survival of NHL patients with LMR for 12, 24 and 33 months were 55.2%, 34.5%, and 5.2% respectively as shown on Figure 8 below.

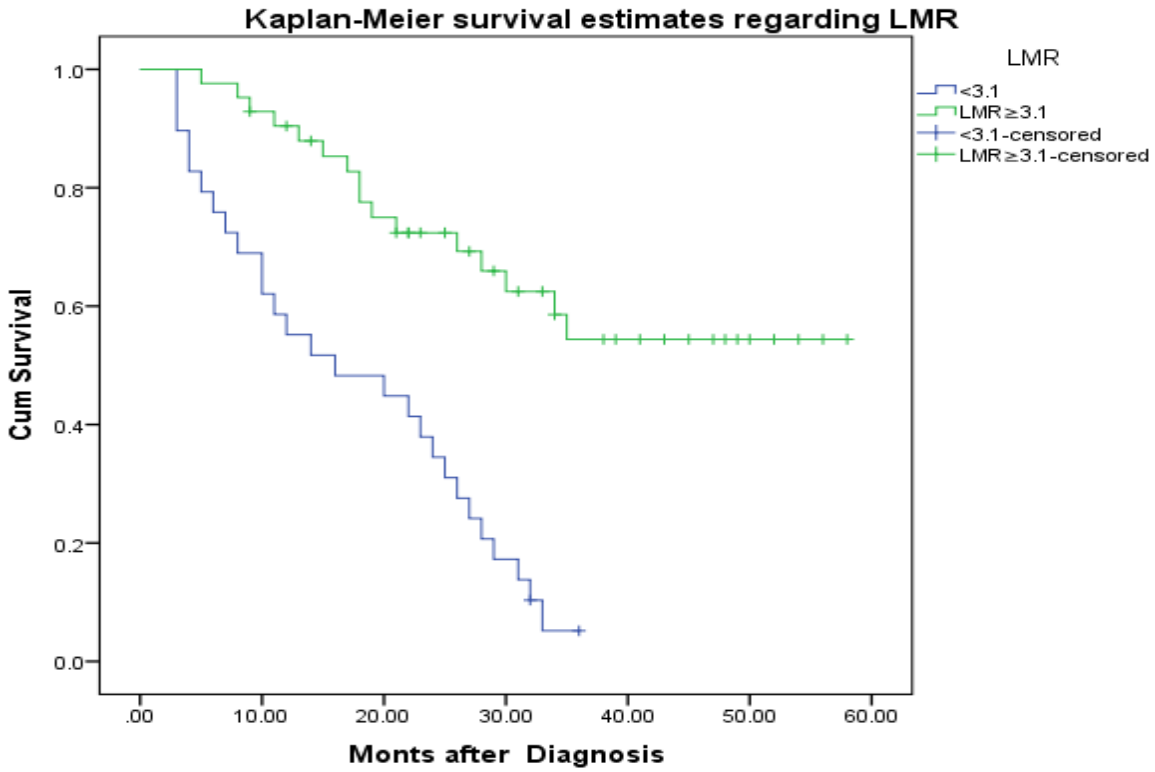

Figure 8: Kaplan–Meier curves for 5-year overall survival of NHL, regarding LMR, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

The anticipated overall survival of NHL patients with PLR <144 for 12 and 22months were 74.9% and 55.3% respectively as shown on Figure 9 below.

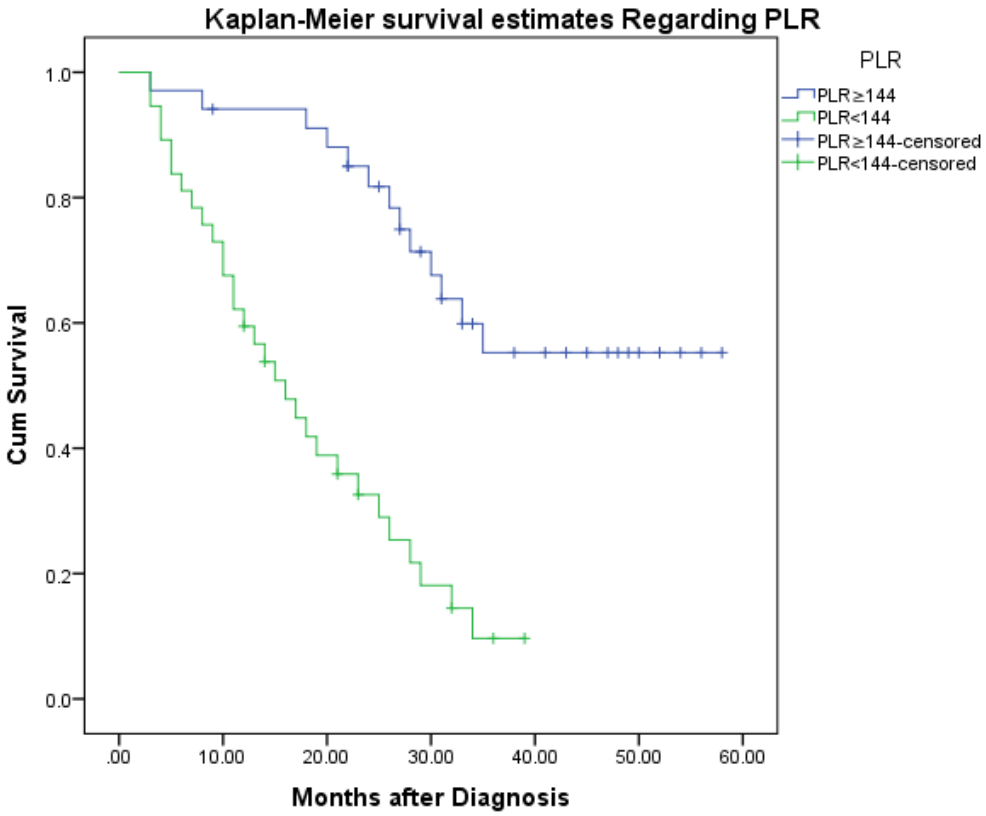

Figure 9: Kaplan–Meier curves for 5-year overall survival of NHL, regarding PLR ≥ 144, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

The anticipated overall survival of NHL patients with NLR ≥ 2.8 for 12, 24 and 32 months were 63%, 43% and 26.9% respectively as shown on Figure 10 below.

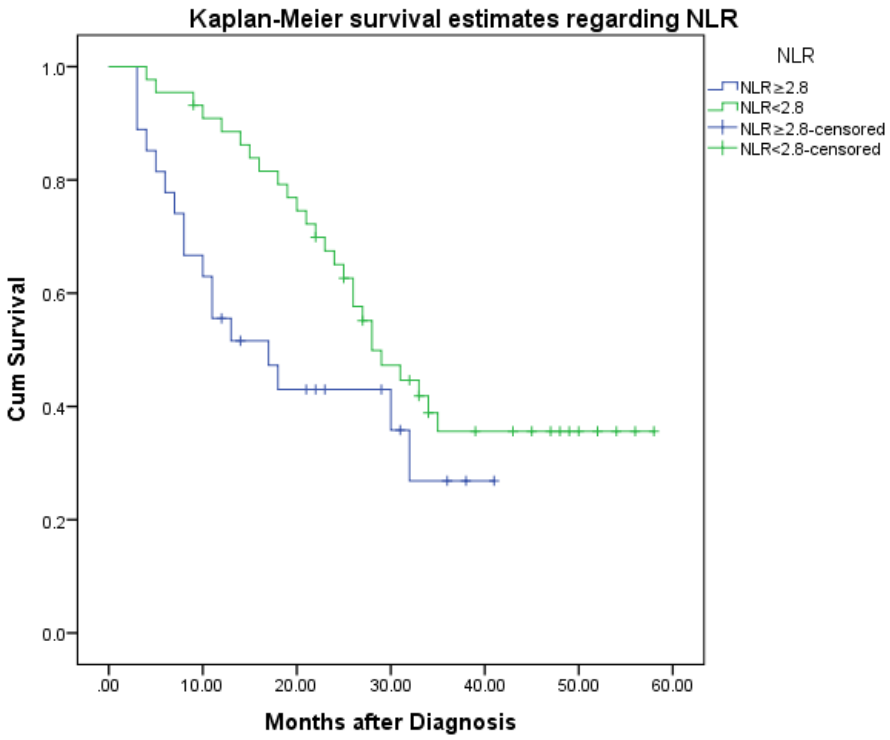

Figure 10: Kaplan–Meier curves for 5-year overall survival of NHL, regarding NLR, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

The anticipated overall survival of NHL patients with stage ≥2 were 67.5%, 38.9, % and 6.9% for 12, 24 and 35 months respectively as shown on Figure 11 below.

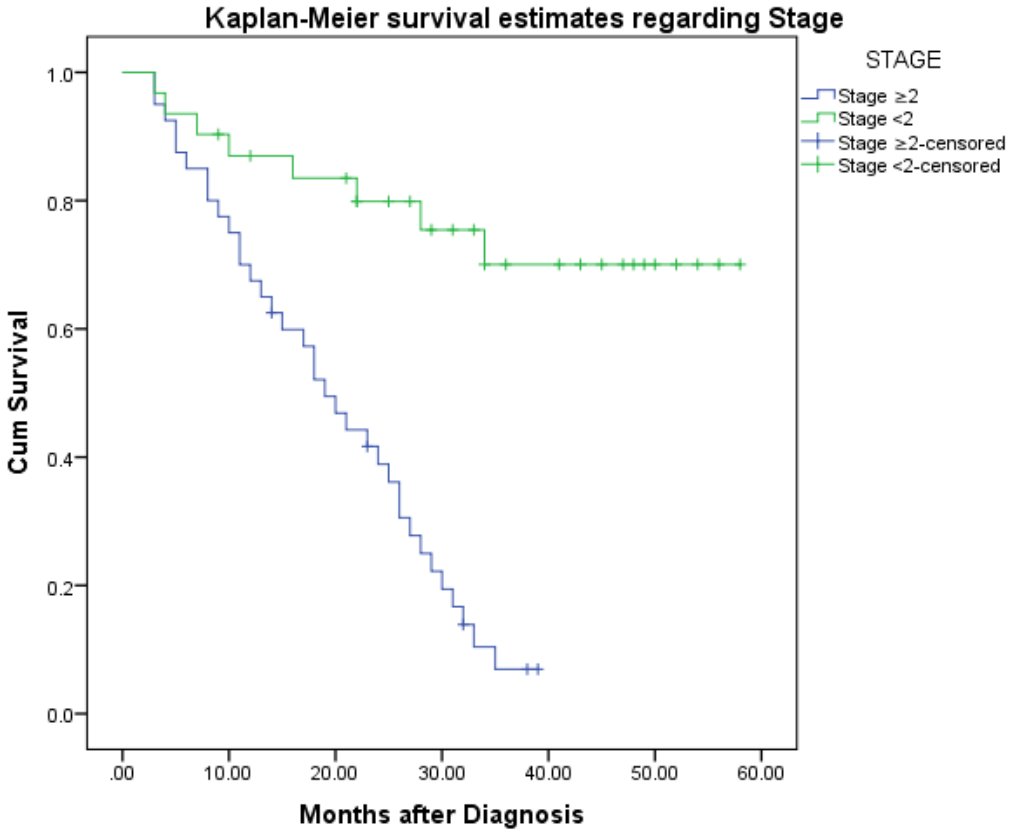

Figure 11: Kaplan–Meier curves for 5-year overall survival of NHL, regarding stage of NHL, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

The anticipated overall survival of NHL patients with CCI≥3 for 12 months was 63.2% as shown on Figure 12 below.

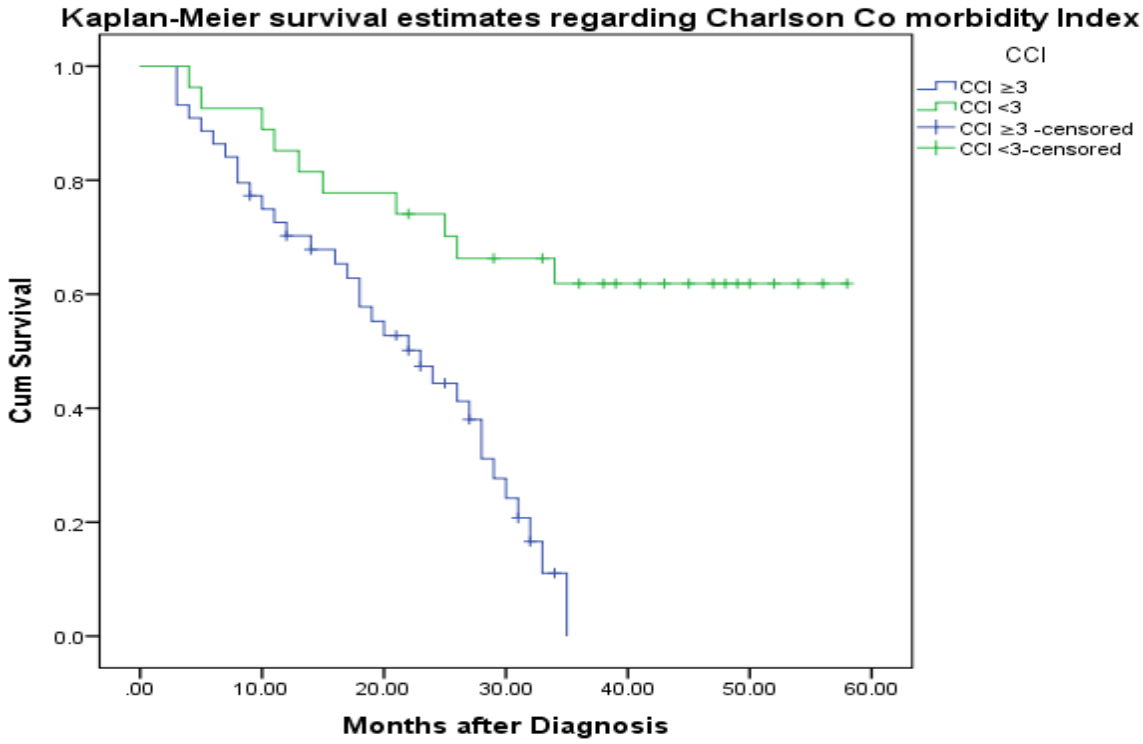

Figure 12: Kaplan–Meier curves for 5-year overall survival of NHL, regarding Charlton Co morbidity Index, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

The anticipated overall survival of NHL patients with LDH ≥245, were 63.3% and 52.6% for 12 and 17 months respectively as shown on Figure 13 below.

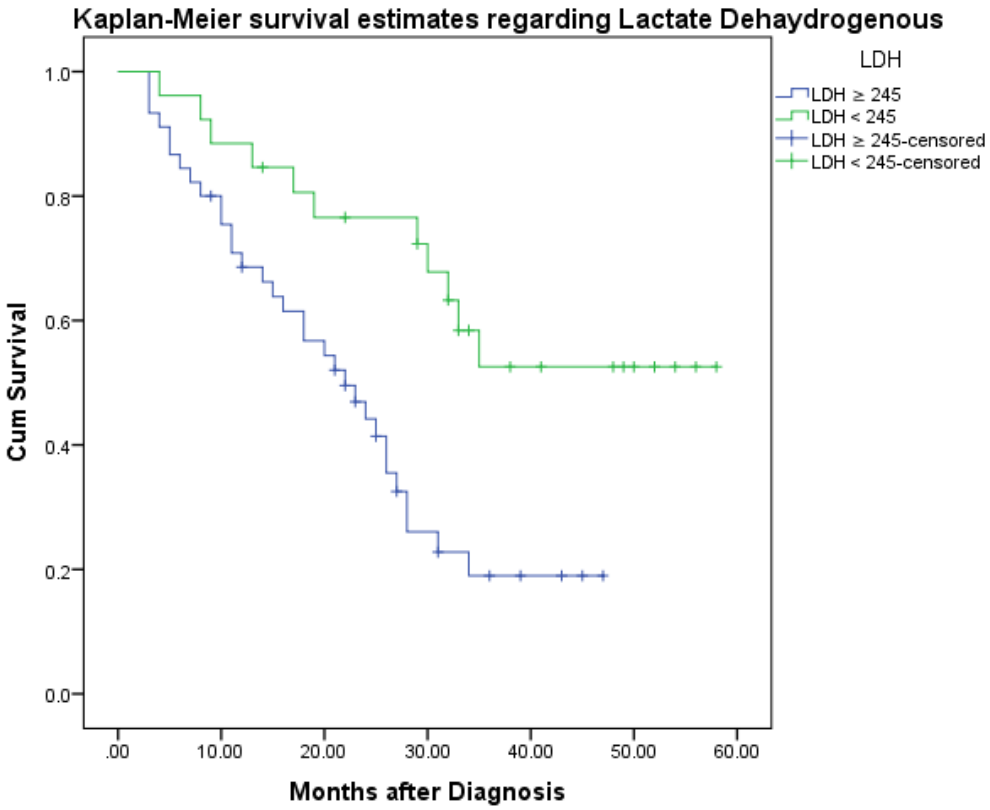

Figure 13: Kaplan–Meier curves for 5-year overall survival of NHL, regarding Lactate Dehaydrogenous, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

5.7. Cox proportional Hazard Model Analysis

Cox Regression analyses were used to assess the prognostic impact of different parameters at diagnosis on the survival of NHL. Each parameter was tested by Bivariant analysis and only those eligible for multivariate analysis (P<0.2) were entered to multivariate analysis.

Table 10: Cox proportional Hazard Model Analysis, for Bivariate and Multivariate association of Overall Outcome and its predictors among NHL patients, at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, from January 2014-2016; N=71

Covariate		**Bivariate**		**Multivariate**	
		CHR [95%CI]	**(P <0.2)**	**AHR[95%CI]**	**(P<0.05)**
Age (years)	≥60	6.6[3.22-13.4]	0.000	2.165[0.44-10.7]	0.34
	<60	-	-	-	-
Stage	≥2	5.7 [2.6-12.5]	0.00	3.3[1.2-9]*	0.018*
	<2	-	-	-	-
Relapse	Yes	6.3[3.3-12]	0.00	6[2-17.2]*	0.001*
	No	-	-	-	-
CCI	≥3	3.4[1.7-7]	0.001	3.5[1.24-9.7]*	0.018*
	<3	-	-	-	-
Lymphocyte count (cell/mm^3)	≤1000	4.2 [2.2-8.2]	0.00	1.46[0.6-3.6]	0.4
	>1000	-	-	-	-
Neutrophil count (cell/mm^3)	≤7500	0.044[0.01-0.2]	0.00	0.6[0.52-1.2]	0.08
	>7500	-	-	-	-
Monocyte count (cell/mm^3)	≥630	5.56[2.8-11.2]	0.00	0.2[0.04-1.06]	0.06
	<630	-	-	-	-
Platelet count (cell/mm^3)	<150,000	2.4[1.3-4.4]	0.007	0.3[0.086-1.014]	0.053
	≥150,000	-	-	-	-
LMR	>3.1	4.2[2.2-8]	0.00	8.8[2-40]*	0.005*
	≤3.1	-	-	-	-
NLR	≥2.8	1.67 [0.9-3]	0.101	4.04[1.12-14.6]*	0.033*
	<2.8	-	-	-	-
PLR	≥144	0.2 [0.1-0.4]	0.00	0.1[0.02-0.4]*	0.001*
	<144	-	-	-	-
LDH	≥245	1.7 [0.9-3.4]	0.16	4.7[1.7-13.2]*	0.003*
	<245	-	-	-	-

CHR-Crude Hazard Ratio; AHR Adjusted Hazard ratio and *- significant association

6. DISCUSSIONS

This study assessed the outcome of NHL at Tikur Anbessa Specialized Hospital; and estimated that the overall five year survival for all types and stages of NHL patients was 32.1%. This finding was extremely lower than five year NHL survival in most developed countries like USA, which is 71%(58), 74.9% in china (29) and 70% in Hong Kong(13); yet it was higher than Gabon and Uganda, where five year survival for all types of cancer was not more than 22% except for breast cancer and 13%(59) respectively. The lack of cancer prevention and control policy, scares information, expensive cancer treatment, in accessibility of cancer centers, insufficient numbers of trained health professionals, and more over less attention to palliative care in most developing countries including Ethiopia, might be the reason for poor survival rate compared to developed countries.

On the present study advanced age, Lymphopenia, higher platelet and monocyte count were poor prognostic indicators while higher neutrophil count was associated with improved survival on Bivariate Cox analysis. On multivariate analysis LMR<3.1, NLR>2.8, relapse, stage ≥2, LDH> 245 and CCI≥3 were identified as independent poor NHL outcome predictors, where as PLR>144 was estimator of enhanced survival.

According to this study LMR predicted overall survival independently among NHL patents. That is having LMR < 3.1 increased mortality risk by 8.8, compared to those who had ≥3.1 LMR, with overall five year survival of 5.2% and 54.4%, respectively. This estimation was in line with other studies in spite of different cut off points; as lower LMR found to increase hazard of mortality by 2, 3.1 and 3.66 times, among different NHL patients with cut off point of 2,3 and 3.2 respectively (28, 43, 47). LMR is an outstanding prognostic bio marker, which mirrors the association between host immunity and tumor microenvironment; as a result low LMR at diagnosis is generally related to hostile disease nature and to poorer tolerance to cancer treatments. It is caused by low LC (Lymphocye count) and/or high MC (Monocyte Count) on peripheral blood count. In addition to NHL, LMR showed to have prognostic value in different malignancies including HL (Hodgkin's Lymphoma), gastric cancer, lung cancer, and colorectal cancer on proceeding investigations (30).

Due to the defensive effect of lymphocytes as part of the immune surveillance system, their increased number helps to prevent excessive tumor growth, yet cancer patients frequently posses severely reduced lymphocyte count (14). Although Lymphopenia happen to predict mortality among French Lymphoma, Carcinoma and Sarcoma patents independently, with 1.48 times increased hazard of mortality among patients having Lymphocyte count <1000 (cell/mm^3) independently (14); it predicted poor prognosis of patients from NHL with 4.2 times higher risk of mortality among lymphopenic patients dependently, on the current study. This may be due to the higher prevalence of other good prognostic indicators like increased platelet count.

Neutrophil Lymphocyte Ratio is reported as mortality predictor on several types of cancer together with, NHL, Gastric and Colorectal cancer (42). On current study, NLR is found to be independent predictor of mortality, with 4 fold augment on risk of mortality among patients having NLR ≥2.8 than those having NLR<2.8. Despite differences on the population and cut off points, this result was consistent with other studies conducted in Hong Kong NLR>2.18, Australian NLR> 4 and Taiwan NLR>4.35 with 1.56,2.02 and 2.31 times higher hazard of mortality compared to patients having <2.18, <4 and <4.35 NLR respectively (13, 41, 42). This might be due to the higher prevalence of Lymphopenia among died patients 30(69.8%) compared to censored ones 4 (14.3%).

Various studies anticipated that Platelets might cooperate in tumor spreading and growth, on anti inflammatory process. As a result in many cancer patients the platelet count is usually higher, while the number of lymphocyte count is lower (31). In this study patients having PLR ≥ 144 had better chance of overall five year survival 55% than those having PLR <144 with 9.7% of five year OS; on the other hand patents who had PLR≥144 had 90% reduced risk of mortality than those NHL patients with PLR <144, this estimation was reliable with other studies, as a Korean study concluded, that high PLR is one of good prognostic indicator among NHL patients; PLR (<95 vs. ≥95) with 70.2% enhanced chance of five year survival (31).

Lactate De Hydrogenous is an enzyme usually released to the blood stream as a result of cell damage. Even though LDH is not specific for cancer, it is commonly used as biomarker for different types of malignancy including NHL (28, 30, 31). The independent predictive value

of LDH among NHL patients is demonstrated on this study, since patients with elevated LDH> 245U/L, was found to have increased risk of mortality by 4.7 fold, than those with normal serum LDH. This result was found to be reliable with previous studies conducted in Australia and China, which indicated LDH> 200 and LDH>245 had 1.62 and 2.18 times higher hazard of mortality correspondingly (42)(27).

Charlson comorbidity index was found to predict over all outcome of NHL on this study, since the hazard of death was 3.5 times higher among patients with severe co morbidity (CCI≥3). This finding was consistent with, study from China, which illustrated that a high CCI ≥2 score were an independent poor prognostic indicator of lymphoma with 4.12 times increased risk of mortality (35). Also CCI was indicated as an additional determinant of prognosis on study carried out in USA; the median survival duration for those with lower and higher CCI score had significant deviation from the finding of this study. Since, the overall five year survival of patients with lower CCI score (0-2) is 70% and patients with high CCI score (≥3) had the overall five year survival of 51% with a median survival duration of 136 and 50 months respectively in USA(35); yet the median survival of patients with CCI<3 and ≥3 was 23 months and 36 months; with the five year survival probability of 00 and 61.9% , respectively.

Although there is substantial difference in socioeconomic status and lifestyle between the populations, this substantial variation in the median survival rate may owe to the in adequate management, and lack of fitting attention for non communicable diseases on the health strategy; since non communicable disease like diabetes and cardiovascular diseases ranked as 2^{nd} and 3^{rd} co morbidity on this study next to HIV accounting for 28%, 26% and 31% of co morbidity correspondingly.

Stage ≥2 and relapse are independent predictors of overall survival among adults with NHL on this study with 3.3 and 6 times increased hazard of death respectively. This finding differs from study in USA which determined advanced stages (stage III and IV) as poor progress free survival indicators with 1.5 times increased hazard of mortality; without any association with overall survival(15). This may account to common presentation of patients at advanced stages stage III and IV in TASH.

7. CONCLUSIONS AND RECOMANDATIONS

7.1 Conclusions

The result of this study found that admission LMR, NLC, PLC, relapse, CCI, Stage and LDH are independent predictors of NHL outcome. This finding may help clinicians to stratify patients in our setting as the parameters are cost-effective and can be applied to every lymphoma patients. Careful evaluation of these factors during admission could help professionals to predict the outcome and act accordingly, in order to provide quality care and improve survival.

7.2 Recommendations

Recommendations for different stake holders founded on the results of this study:

For Researchers

- Future studies may aim to understand more about different sub types of NHL as well as patients on different therapeutic regimens, Prospectively
- Multi institutional studies with larger sample sizes are highly suggested.
- Progress free survival assessment is also recommended, for better prediction of prognosis

For Hospitals

- Organizing team for better management of patients, especially those with co morbidity is strongly recommended.

For Health Professionals

- Clinicians are strongly recommended to stratify patients, based on the possible prognosis in order to initiate end of life care.
- Nurses should advocate early initiation of palliative care, when needed

For Ministry of Health

- Ministry of health and other stake holders should work on expanding the treatment of hematological malignancies to benefit middle and low income families and rural residents.

- Additionally, expanding hospice and palliative care services and equipping health care providers with adequate knowledge and skill about palliative and end of life care is so important in order to reduce the number of lost follow ups.

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9. APPENDIX

Annex I: information sheet

Title of the Research proposal: Outcome of patients with non Hodgkin's lymphoma and its predictors, at Tikur Anbessa Specialized Hospital: A retrospective chart review; Addis Ababa, Ethiopia, 2019

Name of Investigator: Bruktawit Tadesse
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 unit, Addis Ababa, Ethiopia. The aim of this form is, to be clear about the purpose of research with the concerned office about data collection procedures and to get permission in order to conduct the study.

Purpose of the Research thesis: is to assess Outcome of patients with non Hodgkin's lymphoma and its predictors, at Tikur Anbessa Specialized Hospital: A retrospective chart review; Addis Ababa, Ethiopia, 2019

Procedure: In order to achieve the above objective, information, will be taken from medical records of patients' with hematological malignancies from January 2014 to January 1015. Patients' and relatives might be contacted by using telephone for further information and to obtain consent to use their charts.

Risk and /or Discomfort: As this study is retrospective and non interventional; it will not inflict any harm on the study participants. The Privacy, confidentiality and anonymity will be guarded; and the scientific objectivity of the study will be maintained with honesty and impartiality.

Benefits: the study participants will not benefit from this study directly; but as the result of this study will help Nurses and other Health Professionals to stratify and treat patients' based on specific patient status and possible outcome, they may benefit indirectly.

Confidentiality: To ensure confidentiality the data will be collected by nurses working at hematology unit; and the participants name will not be mentioned, instead it will be coded and entered to secure software.

Person to contact: This research project will be reviewed and approved by the institutional review board of Addis Ababa University College of Health Sciences, School of Nursing and Midwifery. For further information, the followings can be contacted:

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Annex II: Data Collection Tool

Name of data collector---------- Date of data collection----------

Code of patients chart ----------

Socio – demographic related factors

Sr. No.	Questions	Response and categories	Remark
101	Age (years)	----------	
102	Sex	1. Male 2. Female	
103	Marital Status	1. Single 2. Married 3.Separated 4. Windowed 5.Divorced	
104	Region	1. Oromiya 2. Amhara 3. Tigray 4. Others	
105	Place of residence	1. Urban 2. Rural	

Outcome of Hematological malignancy

Sr. No.	Questions	Response and categories	Remark
201	Outcome	1. Death 2. On follow ups 3. Lost to follow ups	

202	Follow up duration	In month _____	

Disease related factor

Sr. No.	Questions	Response and categories	Remark
301	Type of NHL	_____	
302	CCI (Charlson Co morbidity index)	_____	
303	Relapse	1. Yes 2. No	
304	Stage of malignancy	_____	
305	Sepsis	1. Yes 2. No	

Patient related (Hematological, Performance and Lactate De hydrogenous) related factors

Sr. No.	Questions	Response and categories	Remark
401	White blood cell count(cell/mm^3)	_____	
402	Hemoglobin count (g/dL)	_____	
403	Platlate count (cell/mm^3)	_____	
404	Lymphocyte count(cell/mm^3)	_____	

405	Monocyte count(cell/mm^3)	_____	
406	Neutrophil count (cell/mm^3)	_____	
407	ECOG performance status	_____	
408	LDH (U/L)	_____	