
**ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF NURSING AND MIDWIFERY, DEPARTMENT OF NURSING, POST GRADUATE PROGRAM**

# Survival status and predictor of mortality among breast cancer patients in Black Lion Specialized Hospital Adult Oncology Unit, Addis Ababa, Ethiopia, 2018.

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## STATEMENT OF DECLARATION

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## List of Abbreviations and Acronyms

| | |
|---|---|
| AAU | Addis Ababa University |
| AJCC | American joint committee on cancer |
| ASMR | Age Standardized Mortality Rate |
| BLSH | black lion specialized hospital |
| ER | Estrogen Receptor |
| FMOH | Federal Ministry of Health |
| GLOBOCAN | Global Burden of Cancer |
| HER2 | Human Epidermal Growth Factor Receptor 2 |
| HIC | High Income Country |
| IDC | Invasive Ductal Carcinoma |
| LMICs | Low and Middle Income Countries |
| PR | Progesterone Receptor |
| SSA | Sub-Saharan Africa |

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## Abstract

**Introduction:** Breast cancer is a leading cause of death worldwide, and ranks as the fifth cause of death from all cancers, and the most common cause of cancer death in women in both developing and developed countries. Breast cancer ranks as the first most frequent cancer among women in Ethiopia. In spite of the high incidence and mortality rate, survival status among breast cancer patients is not estimated in our country. Hence, this study aimed to assess survival status and predictor of mortality among breast cancer patients in Black Lion Specialized Hospital.

**Objective:** the main aim of the study is to assess the survival status and predictor of mortality among Breast Cancer patients in Black Lion Specialized Hospital Adult Oncology Unit in 2018.

**Methods:** An institution based retrospective longitudinal study was conducted in BLSH Adult Oncology Unit. All cases of breast cancer registered from January1$^{st}$ 2012-December30$^{th}$, 2014 in BLSH were followed retrospectively for the six-year survival (until december30$^{th}$, 2017). Kaplan-meier survival curve together with log rank test were used to test for the presence of difference in survival among predictor variables. Cox regression were used at 5% level of significance to determine the net effect of each explanatory variable on time to death after diagnosis of breast cancer. Descriptive statistics were used to describe patient characteristics.

**Results:** A total of 627 adult patients with breast cancer were included in the analysis. Of these, 169 patients (26.95%) were died giving a crude death rate of 9.8 per 100 person years (95% CI: 8.49- 11.47).The overall median survival time was 56.5(95% CI (53.46 - 60.83)) months. The overall estimated survival rate after diagnosis of breast cancer was 26.42% (95% CI, 17.09 to 36.67 %) at 72 months of follow up. Independent predictors of mortality were clinical stage (III&IV),(HR =1.86 at 95% CI (1.13- 3.08)), positive lymph node status (HR: 1.83, 95% CI (1.22- 2.736)) and hormone therapy were protective (HR: 0.67, 95% CI (0.45- 0.98)).

**Conclusion and recommendation**: The overall probability of survival in breast cancer patients were inferior when compared with those of high and middle income countries. Significant predictors of mortality in breast cancer patients were advanced clinical stage, poorly differentiated histology grade, surgical margin involvement, positive lymph node status, Absence of hormone therapy, and breast conserving surgery. Hence, a special emphasis should be given to early screening, early stage diagnosis & early initiation of treatment since advanced stage were prone to high mortality.



**Keywords:** Breast cancer, predictors**,**survival

# 1. INTRODUCTION

## 1.1. Background

Breast cancer is a malignant tumor that starts in the cells of the breast and can spread outside the breast, to the lymph nodes under the armpit and then it starts to spread to all body lymph nodes. Most types of Breast cancer start from the inner lining of milk ducts and hence are known as ductal carcinomas, whereas that appear in the lobules so called lobular carcinomas [1]. Breast cancer is a leading cause of death worldwide, and ranks as the fifth cause of death among all forms of cancers, and which is the second most common cancer globally next to lung cancer and which accounts for 25% of cancer cases and 15% of cancer deaths among women worldwide [2, 3].

In US by 2017, an estimated 252,710 new cases of invasive and 63,410 new cases of non-invasive breast cancer and about 40,610 women are expected to die from the breast cancer. More than 1.1 million women globally are newly diagnosed and leads to 1.6% of worldwide female deaths annually from cancer causes [1, 4]. In less developed regions, breast cancer incidence was proportionally smaller, but it is the most frequent cause of death among women, whereas in more developed regions, mortality become decreased [5, 6]. The range in mortality rates with in developed regions is less than the incidence because of the more favorable survival of breast cancer in (high-incidence) developed regions [6].

In 2012, there were an estimated of 6.2 million women worldwide who had survived breast cancer after being diagnosed within the preceding five years. The highest proportion of breast cancer survivors who were observed within the past five years were in the developed country, this is due to the availability of services for early stage at diagnosis in those countries. Whereas there were low proportion of survivor in low and middle income country's( LMICs), because of resources are limited and breast cancer survivorship issues are only recently being addressed[7].Even though White women are slightly more likely to develop breast cancer, African-American women are more likely to die of this cancer [1].

Breast cancer is responsible for one in four diagnosed cancers and one in five cancer deaths among women in Sub-Saharan Africa (SSA). Despite its emerging public health danger, incidence rates are still generally low in Africa[8]. Precise incidence figures in Africa, however, are lacking given

the absence of cancer registration in most countries. According to Global Burden of Cancer (GLOBOCAN) data estimate in 2012, there were, 94,000 women developed breast cancer and 48,000 died from it in SSA. Within SSA, there is considerable regional variation in the estimated incidence of breast cancer, with incidence rates (per 100,000 women) were showed that 30.4 in Eastern Africa, 26.8 in Middle Africa, 38.6 in Western Africa, and 38.9 in Southern Africa [2, 8].

Breast Cancer is an increasing public health problem for Sub- Saharan Africa at large[9]. In Ethiopia, Breast cancer is the most prevalent cancer among women, and constitutes a major public health concern. Although, definite prevalence and incidence studies are lacking in Ethiopia, some estimates indicate that the breast cancer accounts for about 20.8 % of all cancers, which representing approximately 216 cases per annum [10]. As a result, to avert this burden currently the Ethiopian Federal Ministry of Health (MOH) prepared a task force to address the issue of non-communicable diseases particularly with especial emphasis on cancer .One of the fundamentals parts of the strategic framework is to reduce the incidence and mortality of cancer and improve the quality of life of cancer patients[11]. In line with this strategy, this study aimed to assess the survival status and predictor of mortality among Breast cancer patients attending Adult Oncology Unit of Black Lion Specialized Hospital (BLSH).

## 1.2. Statement of the problem

Breast cancer survival were varying greatly worldwide, ranging from 85% or higher (cumulative 5-year survival) in the high-income countries, while it is 60% or lower in many LMICs. By contrast, concerning to Sub-Saharan countries, South Africa 53.4%, Gambia 11.9 % and Mali 13.6% were significantly inferior to other countries around the world [12]. Overall, in high-income countries, breast cancer is often diagnosed at an early stage and the prognosis is good; whereas in LMICs, women presents at a younger age, presents at a more advanced stage with more aggressive histologic characteristics ,and was associated with a worse survival[13, 14].

There were wide global variance in survival from breast cancer, both in developed and developing country, thus, the variation were widest for women who were older, late stage at diagnosis, with missing stage at diagnosis[15], survival at five years were reported higher (84%) in the US than (81%) in Europe. In addition Survival in Northern, Western and Southern Europe (81–84%) was similar to that in the US (84%), but it was lower in Eastern Europe (69%) [16]. Furthermore, another study, indicated that ,5-year survival for breast cancer was impartially close to the European mean of 81·8% [17].

More than half of all new cases of breast cancer diagnosed in the industrialized world, while more than three quarters of breast cancer related deaths occur in the developing countries, particularly Sub-Saharan Africa is the most affected region. Approximately, the 5-year survival estimates of women having breast cancer in SSA revealed that near or below 50% ,in contrasting with 73% and 85% among black and white women in the US, respectively [9].Overall, LMICs had Significant mortality rate than that of high income countries. According to GLOBOCAN data, in 2012, the mortality/incidence ratios ranged from 0.55 in Central Africa to 0.16 in the U.S. As a result, mortality rates appear to be rising in certain LMICs, where as they decline in most high-income countries [18].

Even though there was wide international variation on the survival of breast cancer, currently there is an overall improvement in the globe with the 5-year relative survival rate of 83% for Black women while it accounts 92% for White women.The racial disparity in survival reveals more advanced stage of disease at diagnosis, lack of medical coverage, barriers to early detection and screening, as well as higher rates of more aggressive, and triple negative breast cancer among black women[1]. According to hospital-based multi-center study survival varied significantly by

stage at diagnosis and molecular subtype. Patients with late-stage disease had much lower survival rates than those with early-stage disease; patients with human epidermal growth factor receptor 2 ( HER2) and triple-negative subtype tumors had lower survival rates [19].

Breast cancer incidence in Ethiopia, is relatively high compared to other SSA countries, whereas lower than in most developed regions of the world. Along with World health organization estimation, an age standardize incidence case of breast cancer were 12,956 and mortality rate of breast cancer were 25 per 100 000 women respectively[20] . Despite the extensive knowledge about incidence and survival rates for cancer in the western world, cancer survival data is not widely available from countries in Africa, Asia, and Central America [21, 22] . Breast cancer is the most common cause of cancer deaths among women in developing countries particularly in SSA and survival tends to be poor in this region because of a combination of a late stage at diagnosis and limited access to timely and standard treatment [23]. There is little information on breast cancer survival in Ethiopia and other parts of sub-Saharan Africa[9]. Despite, the government concern on the issue of non-communicable diseases with especial emphasis on cancer, in order to reduce the incidence and mortality, the survival status of breast cancer still were not known in Ethiopia particularly at the BLSH. Hence, this study aimed to assess the survival status and its predictor of mortality among breast cancer patients at Black Lion specialized hospital, Addis Ababa, Ethiopia, 2018.

# 2. LITERATURE REVIEW

## 2.1. Introduction

The aim of this literature review is to summarize what has already been existing knowledge base about breast cancer survival in developing and developed country, to discuss the impact of the research findings to clinical practice, and to identify gaps in Breast cancer patient's survival in Ethiopia. As a baseline, literature have been reviewed and collected on demographic, pathologic, clinical, treatment and other related factors, which have an impact on Breast cancer survival outcome.

## 2.2. Survival status among Breast cancer women

Over all Breast cancer mortality rates vary greatly around the world. It is higher in less-developed countries and minimal in the more-developed countries[24]. Internationally, the burden of breast cancer falls most seriously on developed nations, since it is the most frequent cancer among women, with a mortality rate of 12.9/100,000 women. Yet, the magnitude of those rates may vary across the world, in such a way that mortality rates are almost similar among the developed and developing countries (14.9/100,000 vs 11.5/100,000)[24]. the death rates for breast cancer were significant through racial and ethnic groups which reflect higher among non-Hispanic white 20.8/100,000 and non-Hispanic black 29.5/100,000 women than Asian/Pacific Islander 11.3/100,000 women have the lowest death rates[1].

A study which have been done in Hawaii shown that after a median follow-up time of 13.2+3.7 years, 115 (30.1%) deaths had occurred, 43(37.4%) from breast cancer and 72(62.6%) from other causes .Overall ,survival was high,340 (89%) patients were alive 5 years after diagnosis and 291 (78%) were known to be alive after 10 years [25].A similar study done in Brazil, showed that the mortality rates reveal wide variation, ranging from 0 to 431.8 deaths per 100 000 women-years [26] and a study which have been conducted in Iran revealed, that the possibility of death for patients who are in grades 2, 3 and 4 of the disease, in compare with the people in grade 1 of illness were:1.63, 1.46 and 1.39 with a p value of <0.001[27].

A study of breast cancer survival in sub-Saharan Africa revealed that the age standardize mortality rate of breast cancer per 100 000 women were 25.9 in Nigeria, 16.5 in South Africa, 9.6 in Namibia, and 13.6 in Uganda [9]. Similarly, a study that was carried out in Nigeria founds

(4.74%) cancer death, breast cancer was responsible for most of the deaths and accounted for (28%) deaths[28] .On the other hand a study which have been done in Ghana shows breast cancer-related deaths were (38.16%) among the study subjects [22],which is higher than WHO breast cancer mortality profile in Ethiopia (24.4%)[20]. An observational analytical study which have been done in Uganda founds (23 %) deaths were observed; the majority (of those) who died were stage III [29].

A population-based study which have been conducted in Malaysia and Germany showed that the overall 5-year survival rate were 49.4% and 83% respectively[30, 31] .In addition in Malaysia the median survival time was 68.1months. A study done in Cameroon revealed that the 5 years overall survival rates were (30%) which had been lower than that of Uganda (51.8 %) [29] and had a median overall survival time of 2 (1.9 - 3) years [32]. on the other hand a study done in Egypt and Sudan founds the median overall survival for early-stage breast cancer (stages I and II) had longer than advanced stage(III and IV) at presentation [33, 34]. Similarly, a study done in Sudan shows the median overall survival period was 40 months and the cumulative survival probability was 38% which is higher than Tanzania 21.8%[35].

According to a study which have been conducted in Northwest Iran, shows that one, three, and five years, overall survival rate were about (96%, 86%, and 81%),respectively [36] ,almost which was parallel to that of Brazil ( 90.9%) [37] and western amazon brazil (95.5%, 56 83.7%, and 87.3%)[38]. However, higher than those in other studies, such as that of Vietnam (94%, 83% and 74%),Qidong(83.61%, 67.53%, and 58.75%),and Malaysia (70.8%, 56.9% and 49.4%) respectively[4, 30, 39]. A similar study conducted in Ghana revealed that the overall cumulative 5-year survival was 47.91% along with the mean survival time of 4.59 years (55.13 months). At the time of diagnosis 14.47% of the women had stage 0 & I, and 5.20% stage IV. Among those cases diagnosed stage 0 & I, a 5-year cumulative survival was 91.94% and 15.09% for those stage IV, however, lower than a study done western amazon brazil which is (93.3%,50%) respectively[38]. Tumor grade 1 had 5-year cumulative survival rate of 49.32%, grade 2 was 48.83% ,and grade 3, 40.87% [22].

## 2.3. Predictors of breast cancer mortality

Studies on survival status a among breast cancer patients have been shown that stage of cancer at diagnosis, histological grade and type, age at diagnosis, treatment modality, lymph node involvement and size, receptor status, co-morbid illness determine the survival time of breast cancer. Differences in survival time among breast cancer patients have been reported in different countries and in different studies [4, 25, 40, 41]. Some of the literatures regarding to survival time and predictor mortality among breast cancer are reviewed as follows.

### 2.3.1. Sociodemographic predictors

A study done in Vietnam indicates, married women had a risk of death nearly 1.59 times higher than unmarried women ,education level had approximately 10% hazard ratio compared with those classified as illiterate [4]. Similarly, a study done in Iran shows that age at diagnosis under 40 years (p=0.005), level of education (p=0.004) had a statistically significant effect on survival time[42]. Moreover, a study in Egypt founds that death among rural patients was 2.4 times higher than among urban patients, high vs low educational level was 0.35 hazard ratio, ,and housewives had died nearly 1.5 times higher than skilled patients ,were significantly associated with survival (each $P < 0.0001$) [43] .

Other study, which have been done in Northwest Iran also showed that patients younger than 40 years old had lower survival compared to patients older than 40 years[36] ,whereas a study in Nigeria showed that there was no significant difference in survival in patients who were below 40 years and those above 40 years[44]. Furthermore, population-based study in Malaysia found that women aged less than 50 years old showed significantly better survival compared to women of 50 years old and more years [30]. In addition, different studies which have been conducted in different country showed that age was independent predictors of survival with p-values: of (each $p<0.001$)[25, 31, 39, 45]. A retrospective cohort study and meta-analysis on factors associated with survival of patients with breast cancer in Iran revealed that race, marital status, age in time of diagnosis, and job were investigated as the major predictor of patient's survival ($P<0.05$) [27, 40].

Different institution based studies done in different countries shows that having at least one comorbidities, were associated with a higher risk of dying and shorter overall survival [25, 41,

46]**.** A prospective non-selective cohort study which have been conducted in Nigeria**,** revealed that premenopausal had significant difference in survival than postmenopausal at (p = 0.015) [44], on the contrary other retrospective cohort study done in North Western Nigeria showed that postmenopausal patients (70.6%) had better survival than premenopausal (68.5%) patients at (*p*=0.05)[21].

### 2.3.2. Pathological and clinical predictors

A retrospective cohort studies which have been conducted in Vietnam showed that the hazard ratio risk of death for stage IV was 2.27 times higher than that for stage I [4] . Similarly, population-based survival studies on different country revealed that stage, and tumor grade were independent predictor of breast cancer related excess mortality [31, 47]. The Uganda study found that the hazards of dying were higher for stage III/ IV disease than stage I and II deaths [29]. Similarly, studies in both Cameroon and Honolulu revealed that advanced tumor stage predicted significantly higher breast cancer mortality[25, 32].

A retrospective cohort study conducted in North Western Nigeria indicated that histological sub-type's invasive ductal carcinoma(IDC) was the predictor of mortality[21].Similarly in Ghana a 5-year survival rates were 42.95% for patients diagnosed with IDC as compared to 65.03% for other breast cancer types[22] and Iran study indicates histologic grade ($p<0.001$) were increased the hazard of death [42].On the other hand, a study that have been conducted in Germany, shows that HR(hormone receptor) negative tumors compared to those with HR positive tumors ,which increase 2.9 fold the hazard of death [31].The study done in California revealed that women diagnosed with HR-/HER + and triple-negative breast cancer experienced a 1.6-fold and 2.7-fold increased risk of death than women with HR+/HER2- breast cancer sub type respectively[48].

A retrospective study, done in Ghana, shows that the subjects with the triple negative subtype, ER/PR and HER2-neagive, had the worst overall survival of 50.80% as compared with the other subtypes [22].The Iran study revealed that estrogen receptor (p=0.008), progesterone receptor (p=0.007), had a statistically significant effect on survival time[42] ,and a meta-analysis study which have been conducted in Iran showed a similar findings. Whereas, the death risk of patients with progesterone receptor negative was reported to be more than 1.5 times the patients with progesterone receptor positive [40].

American cancer society cancer facts and figures report shows that the 5-year relative survival is 95% for tumors size less than or equal to 2.0 cm in diameter, 85% for tumor size is 2 to 5 cm, and 72 % for those over 5 cm [1].likewise, a meta-analysis study which have been conducted in Iran revealed that patients with a tumor of 5.0 centimeter and bigger are prone to death twice compared to patients with a tumor of 2.0 centimeters and smaller[40].A hospital based study in Brazil illustrate that tumor size > 2.0 cm were increased risk of death 1.9 times than <2cm tumor size and presence of compromised lymph nodes had been the hazard ratio of 3.7 times [49]. However, a study in Northwest Iran shows that diameter of the tumor had minimal effect to the survival of the patient with breast cancer [36]. The finding from Iran and Egypt indicates that lymph node status ($p<0.001$), tumor size ($p<0.001$) had a statistically significant effect on survival time[42, 43].

Another study in Iran founds the risk of death in patients who had less than two involved lymph nodes was founds 1.5 times higher in comparison with the patients with more than seven involved lymph nodes, ($P$=0.03). As a matter of facts, the risk of death after metastasis in patients with tumor size >5 cm was 2.1 times higher than the patients with tumor size ≤2 cm ($P$ =0.019)[50].Moreover, a study conducted in Ghanaian women indicates the tumor size was found to be a significant effect on survival (P =0.0001) and the expected time to die for those with tumor size greater than 5 cm is hazard ratio of 1.48 greater than those with tumor size less than or equal to 5cm.Regarding the lymph node involvement, there was a significant difference between the two (p = 0.0003) with the hazard ratio of 2.54 [22]. On the other hand a study in Egypt founds that metastases to bone has the hazard of death of 3.2, and metastases to lung has the hazard of death 2.3, were all significantly associated with poorer survival compared to the patients without distant metastasis [43]. On the contrary a study in Northwest Iran shows that skeletal metastasis had better survival [36].

### 2.3.3. Treatment related predictors

A finding from British, Columbia, and Canada study shows that in the group of patients under age 50 years old and over age 50 with stage I cancer, the highest hazard was related to radiotherapy which is 3.15, and chemotherapy is also 3.0, respectively. Whereas patients under age 50 years old and over age 50 with stage III and IV breast cancer, in this group, the patients who received surgery had lower hazard of 0.49, and hazard ratio of 0.64.This implies surgery were associated with increased survival rate of patients with stage III and IV cancer[47]. Another

study done in Vietnam indicates women who received hormone therapy had approximately 80% risk reduction of death than those without hormone therapy[4].

A meta-analysis study in Iran shows patients going through surgical operation as their first option survived more than the one who first received chemotherapy[40]. A study ,in Brazil revealed that chemotherapy was not statistically associated with longer survival, whereas among those who use of hormone therapy have a statistically significant protective effect with the hazard ratio of 0.59 [45]. In contrary, a study done in France found Chemotherapy was associated with a 25% reduction in the relative risk of death compared with the untreated group[51]. According to the findings from Cameroon survival was significantly higher in the group of patients who underwent breast conserving surgery compared to those who underwent radical mastectomy [32]. Furthermore, a study conducted in Northwest Iran shows patients who had undergone lumpectomy correspondingly have smaller tumor size, have been higher survival rate compared to mastectomy patients[36], and another Iranian study revealed that type of surgery done, had a statistically significant effect on survival time[42].

In summary, few studies have examined breast cancer survival in sub-Saharan Africa compared to developed populations; all of these report poorer survival among low-income people. Fewer still have examined potential factors related to the poorer survival, but these often suggest poorer prognosis. Breast cancer patient advanced stage at diagnosis, large tumor size, hormone receptor negative are generally at significantly higher risk of death. Possible factors associated with poorer survival of breast cancer, such as: comorbidity, stage at diagnosis, tumor characteristics and treatment, and was not examined among breast cancer women in Ethiopia. Hence, the intention of this research is to asses' survival status of breast cancer and suggest concrete recommendations that could be relevant to government and patient to control breast cancer, improve survival among women in Ethiopia.

## 2.4. Conceptual framework of the study

The conceptual framework shown below is set out from different literature developed for studying in developing countries. It shows the effect of independent variables (individual level predictors, pathologic and clinical, treatment related predictors) on dependent variable (time to death). The development of conceptual framework is based on the following grounds. First, in countries where conditions for breast cancer survival are good, more than 85 % of breast cancer

patients are estimated to survive through the first five years of life is considered. However, this condition is less likely to be met in Sub-Saharan Africa, where the survival of breast cancer is range from 45 and 57.6 % to survive the first five years of life.

Second, any reduction in the proportion surviving in any society is due to the effect of socioeconomic, clinical and treatment factors is considered. Third, which focus on independent variables, particularly personal level predictors, has both direct and indirect influence on the outcome of disease process on their own; and they could also operate through the more basic proximate predictors, which include clinical, histopathological, and treatment related factors. Finally, the dependent variable in the study of breast cancer survival (time to death) are the cumulative results of multiple predictors (developed from different literatures **[9, 21, 22, 28, 29, 43, 44]**. This study will have addressed survival status and predictors of mortality among Breast cancer women in BLSH.

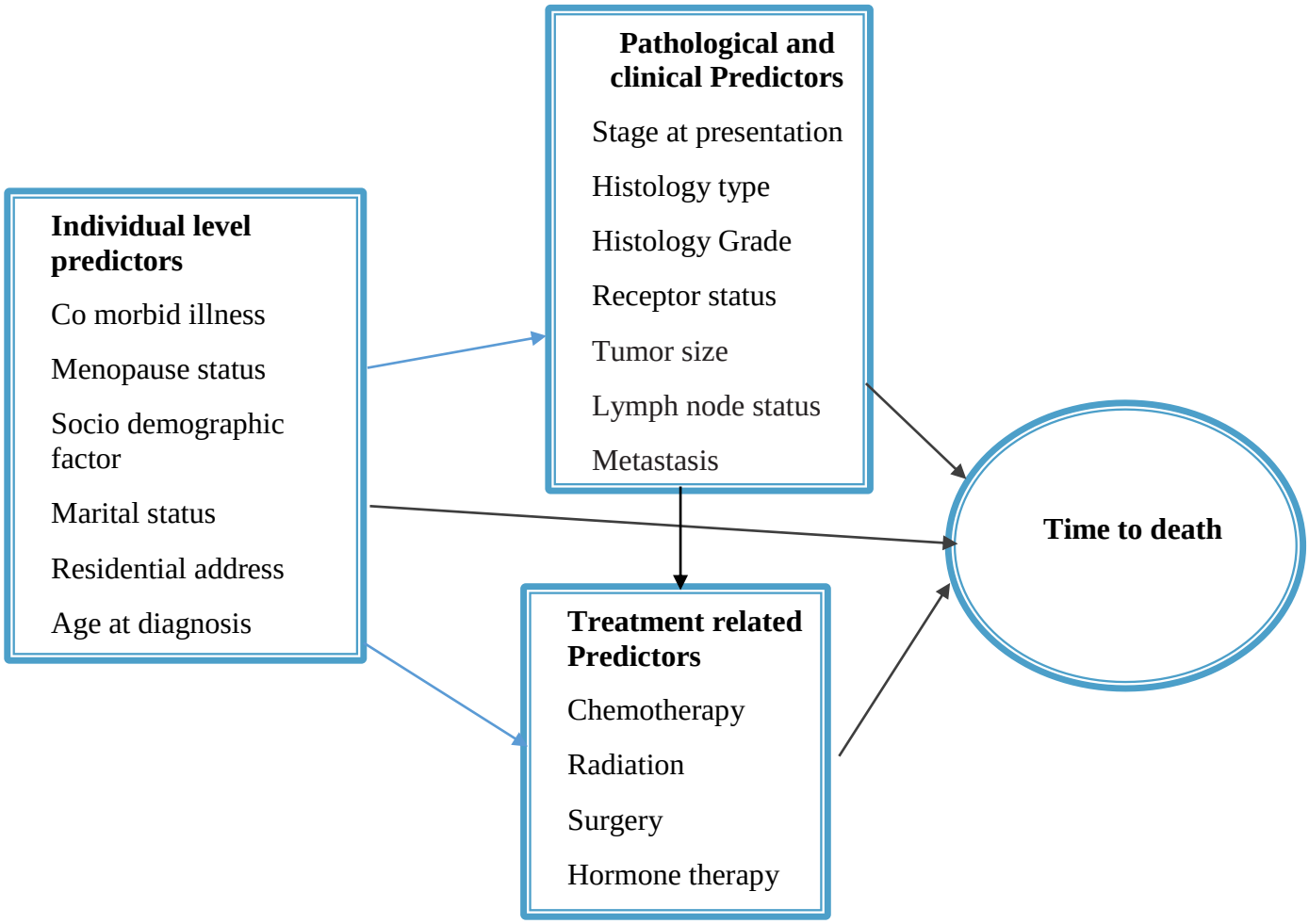


Figure 1:-Conceptual framework for the assessment of survival status and predictors of mortality among breast cancer patients at BLSH, AA Ethiopia, 2018.

## 3. JUSTIFICATION OF THE STUDY

The main aim of this research is to assess survival status and predictor of mortality among breast cancer women in Black Lion Specialized Hospital. Due to the increasing pattern of the disease, high incidence of death, advanced stage of diagnosis, and variation in survival rates across Sub Sharan Africa, the need to measure survival status of breast cancer is apparent. Different studies have been reported a wide variation in the incidence of death among breast cancer across a globe and have documented substantial disparities in breast cancer survival in relation to various predictors. Similarly many study, were limited to only a few clinical and therapeutic predictor of survival over time in a single research. Over all, little had been examined the major determinant of breast cancer mortality.

Despite, the government concern on the issue of non-communicable diseases with especial emphasis on cancer to reduce the incidence and mortality of cancer, the survival status of breast cancer still were not known in Ethiopia. Even though, different studies were conducted on prevalence of breast cancer, pattern of breast cancer, factors on delay in diagnosis. But, none of them did not investigate the survival status of breast cancer in BLSH. Therefore, they may not be representative of the entire women diagnosed with breast cancer. This emphasis to determine thus predictors, time to death and outcomes of breast cancer and which emphasize the extent to which these disparities will explained by stage at diagnosis, first course treatment, rural/urban residence by taking account of these variables. Finally, this study aimed to assess the survival status and predictor of mortality among breast cancer patients at Black Lion specialized hospital, Addis Ababa, Ethiopia.

## 4. SIGNIFICANCE OF THE STUDY

The rational of studying survival status of breast cancers will have practical vital value for patients, providers, researchers and policy-makers in the Ministry of Health. This study will help both society and the individuals at large, to assessing progress in cancer control, including the effect of early detection, diagnosis, and follow-up on breast cancer outcomes. The study will be an input to policy makers, program managers, health professionals in order to estimate survival rate of patients, to decide based on evidence about breast cancer and to support the planning of systems for enhanced cancer control and prevention program.

This paper will also provide insight for Nurses in cancer treatment centers to know the quality and effectiveness of care they provide. Furthermore, knowing breast cancer survival outcome facilitates the initiation of personalized treatment reduces unnecessary treatments, and more precise decision making for both clinicians and patients**.** This will promote nursing research, nursing education and clinical practice so as to provide evidence based nursing care based on new existing knowledge and estimation of prognosis will be based on evidence and local circumstances. Finally, this paper will also be a base line for future researchers.

# 5. OBJECTIVE

## 5.1. General objective

- To assess the survival status and predictors of mortality among Breast Cancer patients in Black Lion Specialized Hospital Adult Oncology Unit, Addis Ababa, Ethiopia, 2018.

## 5.2. Specific objectives

- To assess the survival status of Breast cancer patients in Black Lion Specialized Hospital Adult Oncology Unit Addis Ababa, Ethiopia,2018.
- To determine time to death of Breast cancer patients in Black Lion Specialized Hospital Adult Oncology Unit, Addis Ababa, Ethiopia,2018.
- To identify predictors of mortality among Breast cancer patients in Black Lion Specialized Hospital Adult Oncology Unit, Addis Ababa, Ethiopia,2018.

# 6. Methods & materials

## 6.1. Study area and period

The study was conducted among Breast cancer women in Black Lion specialized Hospital Adult Oncology unit between March 1st to April 28th, 2018 in BLSH, Addis Ababa, Ethiopia.

Black Lion specialized Hospital, is found in Addis Ababa city, the capital of Ethiopia. It is a teaching; central tertiary comprehensive referral hospital has approximately more than 800 beds, give diagnostic, and treatment service for about 370,000-400,000 patients per year. It is the largest and best-known public hospital, which was built in the early 1960's. The BLSH is of the only specialized hospitals in the treatment of cancer in Ethiopia.

It has a number of services specialized in the treatment of cancers such as radiotherapy, medical oncology, anatomic pathology, nuclear medicine, gynecology and surgery. In BLSH oncology unit, there were three senior oncologists, one palliative care specialist, nine residents, five radiotherapist, four medical Physicist, and twenty-three nurses. The most common cancer cases seen in this hospital were breast, cervical, colon and sarcomas. This study was conducted at the oncology unit which is one of the specialty units of the hospital [52].

## 6.2. Study design

A six-year institution based, retrospective follow up study was conducted at BLSH. Patients who have been newly diagnosed and enrolled in breast cancer treatment, from January1st 2012 to December31th2014 at BLSH were followed until the end of the study (December 31th 2017).

## 6.3. Population

### 6.3.1 Source population

All medical records of all adult women diagnosed with Breast cancer in Black Lion Specialized Hospital, Adult Oncology Unit.

#### 6.3.2. Study population

All medical records of breast cancer patients who attended the oncology unit of BLSH from January1st 2012 to December31th2014.

### 6.3.3. Sample population

All medical records of breast cancer patients who attended the oncology unit of BLSH from January1st 2012 to December31th2014 and who fulfill the inclusion criteria of the study

## 6.4. Eligible criteria

#### 6.4.1. Inclusion criteria

- All adult breast cancer patients who were newly diagnosed and enrolled in BLSH during the required time (i.e. January1st 2012 to December31th2014) was included.

#### 6.4.2. Exclusion criteria

- Whose medical charts were incomplete and not found.
- Patients had not previous diagnosis of breast cancer.
- A patient who had diagnosis at other hospitals and referred to the BLSH for further treatment was not included.

## 6.5. Sample Size and Sampling Procedure

#### 6. 5.1. Sample size determination

All breast cancer patients who attended the oncology unit of BLSH from January1st, 2012 to December 31th, 2014 and fulfilled the inclusion criteria of the study was included in the study. This period was selected in order to have the nearest six year follow up study period. A total of 1,083 Breast cancer patient were registered in this period. Hence, 627 patients who fulfilled the inclusion criteria was included in the study.

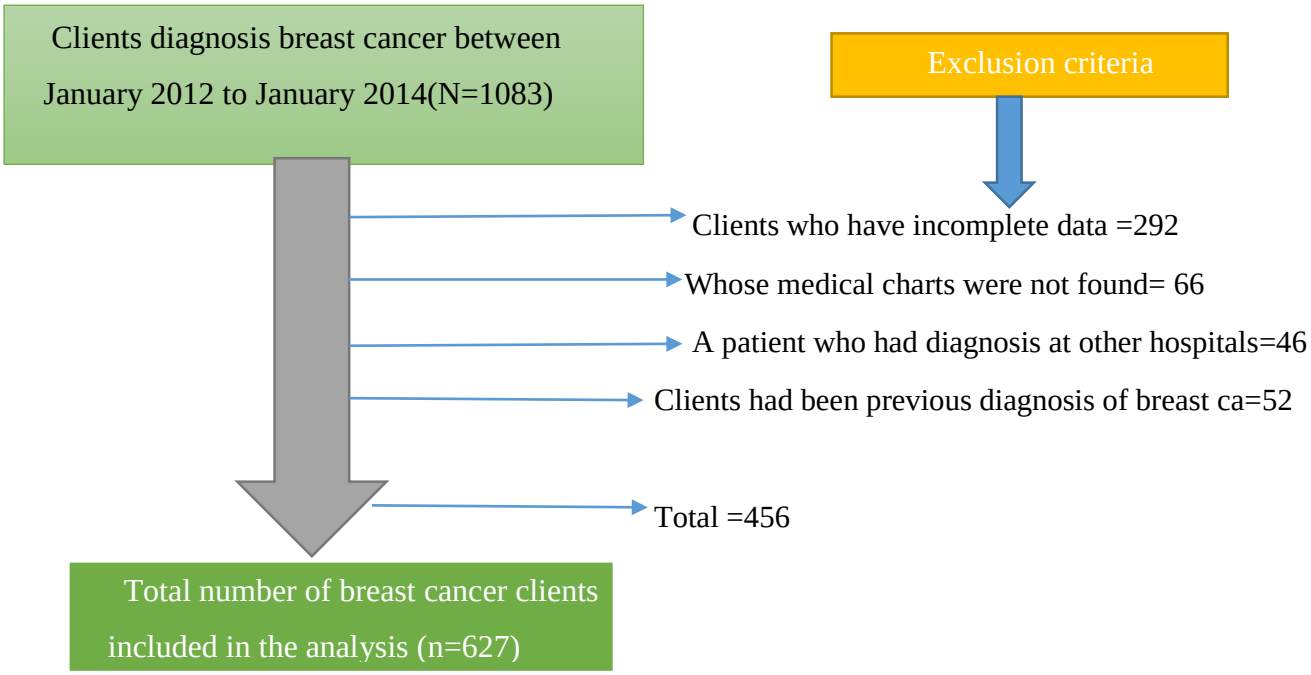


Figure 2:-Diagram showing the final sample size included in the study between January 1st 2012 to December 31th 2014.

### 6.5.2. Sampling procedure

At the beginning, profiles of all breast cancer women on follow up between January 1st 2012 to December 31st 2014 in the BLSH was assessed. Study participants who fulfilled the inclusion criteria in the study were identified by data collectors from list of breast cancer charts who were on cancer care/treatment follow up from BLSH oncology unit. Finally, all samples were selected starting from January 2012 and December 2014 which is census sampling was used.

## 6.6. Study Variables

### 6. 6.1. Dependent variable

- Time to death

### 6.6.2. Independent variable

- **Individual level predictors**
  - Co morbid illness
  - Menopause status
  - Socio demographic factor
  - Educational status

Marital status

Residential address

Age at diagnosis

- **Pathological and clinical Predictors**

Stage of cancer at diagnosis

Histology types

Histologic grade

Hormonal receptor status

Tumor size

Lymph node status

Metastasis

- **Treatment related Predictors**

Type of initial treatment

Chemotherapy

Radiation

Surgery

Hormone therapy

## 6.7. Operational Definition

**Censored;** were those breast cancer women who didn‘t develop the outcome of interest (death) at the end of follow-up period as well as those lost to follow-up or transfer to a different care unit during the study.

**Comorbidity**:- The disease conditions from the Charlson index that have been used in the breast cancer survival literature were taken during data collection [25, 41] . The presence of any of these conditions at diagnosis was designate a „yes‟, while the absence of these conditions at diagnosis will be denoted as „no‟.

**Event;** the occurrence of death from first confirmed diagnosis of breast cancer to the end of the study.

**Incomplete card:** when one of the independent variable was not registered (clinical stage, histologic type and comorbidity status…)

**Index date and closing date to follow-up:-**The index date is the starting date for calculation of survival, and this was the first date of unequivocal diagnosis of breast cancer (January1$^{st}$ 2012 to

December31st, 2014). Closing date is the last status of the patient on the follow up it could be death, censored or ending date to follow up (December31st, 2017).

**Survival status.** In this research, survival status is defined as the outcome of patients were dichotomized into censored or death that is sourced from patient clinical data file from scheduled and unscheduled return visits.

**Time to death**: time to death was calculated at the time (in months or completed years) between the date of unequivocal diagnosis of breast cancer to the date of death, or the closing date.

**Stage at diagnosis**: The American Joint Committee on Cancer TNM classification scheme for staging breast cancers was used [22]. In this research, the coding for those diagnosed at stages I and IV remained. Stages IIA and IIB were collapsed as stage II, and stages IIIA, IIIB and IIIC were collapsed as stage III. All staging information mentioned within the first 3 months after primary diagnosis was used.

## 6.8. Data Collection Tools

A data abstraction format develop from different literature and Addis Ababa city cancer register was used to collect data and necessary information from patients' medical files and the records section in the cancer center of the BLSH .Senior experts to the area of study for content validity examined the checklist. Data abstraction is designed based on study objectives, and contain three parts; 1.checklist related to socio-demographic information and comorbidity condition;2. checklist related to clinical and histopathological factors 3.checklist related to treatment factors and survival status which collected from medical records. Socio demographic information contains 8 items with multiple choice response format, clinical and histopathology part contains 18 item with multiple choice and yes or no response format. Treatment factors and survival status of client on last follow up contains 8 items.

Clinical stage at diagnosis was assigned to each patient by using America joint committee on cancer (AJCC Cancer Staging), Histological grade of breast cancer was assessed by the Nottingham Grading System ,grade (1-well differentiated / 2 moderately differentiated / 3-poorly differentiated / undifferentiated). Tumor size was categorized in accordance with American Joint Committee on Cancer (AJCC) guidelines (≤2 cm, >2–5 cm, >5cm), axillary node status, age at diagnosis, treatment modalities**,** Hormonal therapy, histology type, Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal growth factor Receptor 2 (HER2) status will

be included in the tool. The time (measured in months) to the death was used for the survival analysis.

## 6.9. Data Collection Procedure

All available information on patient records were checked and formats from different literatures were reviewed with modification then appropriate data extraction format was adopted in English in order to extract all the relevant variables to meet the study objectives from patient charts. The starting point for retrospective follow-up was the time from first confirmed diagnosis of breast cancer and the endpoint was date of death, date of lost to follow up, date of last contact until January 31th, 2017.

All charts of breast cancer patients, diagnosed in between January1$^{st}$ 2012 to December31$^{st}$ 2014 at BLSH was reviewed from cancer registries. The record of all study participants were select according to the eligibility criteria. The survival status of patients were obtained from the medical record. Survival time was calculate as the time between the date of diagnosis of breast cancer to the date of death, or the end of study. Before collecting the data, the records were reviewed (both baseline and follow up records), death certificate complemented by registration was identified from their medical record number. Then, the data collectors who were working at the cancer treatment center extracted and reviewed the charts.

## 6.10. Data Quality Control

To ensure quality of the data, Pretest was conducted with 5% of the sample population and data abstraction format, was check to the hospital documentation system to ensure the agreement of the data abstraction format with the need of the study. Any error found during the process of checking was correct and modification was made into the final version of the data abstraction format. Senior experts to the area of study for content validity examined the checklist .Training on record review was given to data collectors and supervisors for 01 days before actual data collection task on the already existing records half day theoretical and half day practical training. Training guide was prepared to facilitate the training. Data quality was control by designing the proper data collection materials, through continues supervision. All completed data collection form was examine for completeness and consistency during data management, storage, cleaning and analysis. The data was entered and cleaned by principal investigator before analysis. Three oncology nurses, who were work on oncology unit, collected the data. The principal investigator of the study was control the overall activity.

## 6.11. Data Analysis Procedure

Data was coded and then, cleaned, entered, edited using EPI-data 3.1 [53] and transferred to STATA 14 statistical software for analysis [54]. Data exploration was undertaken to see if there are odd codes or items that were not logical and then subsequent editing was made. Summary statistics were carried out to describe the demographics, clinical and follow up data in terms of central tendency and dispersion value for continuous data and frequency distribution for categorical data. Incidence density rate (IDR) was calculated for the entire study period. Subsequently, the number of mortality within the follow up was divided by the total person time at risk on follow up and reported per 100PY. Kaplan-Meier survival curve together with log rank test were used to test for the presence of difference in survival among categories of covariates and log rank test was used to compare survival curves. Cumulative survival probabilities were calculated separately for (stage, tumor grade, and tumor size). Before running the Cox regression model assumption of proportional-hazard and multi-colinearity were checked. Lastly, the outcome of each subject was dichotomized into censored or death.

Bivariable cox regression was first fitted and those independent variables, which become significant on the bivariate regression having p-value $\leq 0.25$ level of significance, were included in the multivariate analysis. Cox proportional-hazard regression was fitted at 5% level of significance to determine the net effect of each explanatory variable on time to death after diagnosis of breast cancer. Cox-proportional hazard model assumption was checked using schoenfeld residual test and variables having P-value >0.05 were considered as fulfilling the assumption. Residuals were checked using goodness-of-fit test by Cox Snell residuals, which is, satisfied the model test.The results of these models were express as hazard ratios (HRs) with 95% confidence interval. Finally, the result of the study was presented with text, graph and table.

## 6.12. Ethical Considerations

Ethical clearance and paper of approval was obtained from Addis Ababa University, College of Health Science, School of Nursing and Midwifery, Department of Nursing Institutional Review Board (IRB). The School of nursing and midwifery was write, official letter of co-operation to BLSH. Then permission was taken from the oncology unit. As the study was conduct through review of medical records, the individual patients were not subjected to any harm as far as the confidentiality is kept. To keep the confidentiality all collected data was coded and locked in a

separate room before entered into the computer. After entered to the computer the data was locked by password, names and card numbers were not include in the data collection format, and the data was not disclosed to any person other than principal investigator.

## 6.13. Dissemination of Result

The result of this study will be submitted to Addis Ababa University College of Health science, School of nursing and midwifery, Department of Nursing and it will be disseminate to other concerned bodies after approval to AAU library, to studied health institution (BLSH). Furthermore, the paper will be present on workshops, seminars and annual nursing association meeting. Finally, the manuscript will be submit to scientific journals for possible publication.

## 7. Result

### 7.1. Socio-demographic characteristics of the study participants

Between January 1st2012 to December 31st 2014, 1083 breast cancer patients were enrolled to Black Lion Specialized Hospital from which, 627 were eligible for this study. Cards of six hundred twenty seven (458 censored and 169 death) breast cancer women were included in the present study. The mean age of participants at the time of diagnosis was 42.61years with SD ± 12.28 years. Slightly nearly half, 279 (44.5%) of the age group was less than 40 years old. About two-thirds, 403 (64.3%) of patients were married; most, 433 (69.1%) of the women was premenopausal (age less than 50 years old); slightly more than one-third, 224 (35.7%) were have preexisting medical problem during diagnosis. More than half, 366 (58.4%) of the participants were urban.The socio-demographic characteristics of the study participants are shown below (**Table 1**).

**Table 1:-**Socio-demographic characteristics of breast cancer patients at black lion specialized Hospital, Addis Ababa, Ethiopia ,from January 1st 2012 to December 31st 2017 (n=627)

| **Covariate** | **category** | **Vital status at last contact** | | **Total No. (%)** |
|---|---|---|---|---|
| | | Censored No. (%) | Death No. (%) | |
| Age in years at timeof diagnosis | <40 | 212(75.9) | 67(24.1) | 279(44.49) |
| | 40-49 | 111(68.09) | 52(31.91) | 163(26.0) |
| | 50-59 | 93(78.81) | 25(21.19) | 118(18.82) |
| | 60-69 | 28(62.23) | 17(37.77) | 45(7.17) |
| | >70+ | 14(64.64) | 8(36.36) | 22(3.5) |
| Placeof residence | Urban | 285(77.86) | 81(22.14) | 366(58.37) |
| | Rural | 173(66.28) | 88(33.71) | 261(41.63) |
| Marital status | Single | 71(76.34) | 22(23.66) | 93(4.83) |
| | Married | 301(74.68) | 102(25.32) | 403(64.27) |
| | Divorced | 63(63.64) | 36(36.36) | 99(15.78) |
| | Widowed | 23(71.87) | 9(28.13) | 32(5.1) |
| Menopause status | Premenopausal | 316(72.97) | 117(27.03) | 433(69.05) |
| | Postmenopausal | 142(73.19) | 52(26.81) | 194(30.95) |
| Preexisting medical diagnosis | No | 323(80.14) | 80(19.86) | 403(64.27) |
| | Yes | 135(60.26) | 89(39.74) | 224(35.73) |

## 7.2. Clinical, histopathological and treatment characteristics

More than half, 357 (57%) of the women were clinical stage III breast cancer at the time of diagnosis. Invasive ductal carcinoma (IDC) was the predominant, 427 (68.1%) histology type of cancer. Nearly half, 304(48.5%) of the histology grade were moderately differentiated; Surgery associated with radiotherapy was the common mode of treatment for patients following diagnosis with breast cancer which accounts, 256(40.8%). More than half, 369(58.85%) of tumor size was less than 2.5cm on presentation, the tumor size ranged from 0.5 cm to 8 cm in diameter with a mean of 2.6cm with SD ±1.48 cm. About two third, 407 (64.91 %) of the study participant were reported receiving hormone therapy. Nearly half, 229(48.11%) of patients had modified radical mastectomy surgery. The Clinical, histopathological and treatment characteristics of the study participants are shown below(**Table 2**).

Table 2:-Baseline clinical, histologic and treatment information of breast cancer patients at black lion Hospital, Addis Ababa, Ethiopia, from January 1st 2012 to December 31st 2017 (n=627)

| **Variable** | **Category** | **Vital status at last contact** | | **Total No.(%)** |
|---|---|---|---|---|
| | | Censored No.(%) | death No.(%) | |
| Stage of breast cancer | I | 21(95.45) | 1(4.55) | 22(3.5) |
| | II | 145(86.82) | 22(13.18) | 167(26.63) |
| | III | 245(68.62) | 112(31.38) | 357(56.93) |
| | IV | 47(58.02) | 34(41.98) | 81(12.91) |
| Histology grade | Grade I | 84(91.3) | 8(8.7) | 92(14.67) |
| | Grade II | 237(77.96) | 67(22.04) | 304(48.48) |
| | Grade III | 137(59.3) | 94(40.7) | 231(36.84) |
| Histology type | Ductal insitu | 136(83.44) | 27(16.56) | 163(26.3) |
| | Invasive ductal | 294(68.85) | 133(31.15) | 427(68.1) |
| | Lobular insitu | 15(75) | 5(25) | 20(3.2) |
| | Invasive lobular | 11(73.4) | 4(26.6) | 15(2.4) |
| Deep surgical margin | Free | 393(80.2) | 97(19.8) | 490(79.28) |
| | involved | 58(45.3) | 70(54.7) | 128(20.72) |
| Node status | Negative | 364(80) | 91(20) | 455(72.68) |
| | Positive | 93(54.38) | 78(45.62) | 171(27.32) |
| Metastasis at time diagnosis | No | 348(87.21) | 51(12.79) | 399(63.64) |
| | Yes | 110(48.24) | 118(51.76) | 228(36.36) |
| Tumor size | ≤2.5cm | 289 (81.17) | 67(18.82) | 356(56.78) |
| | 2-5cm | 152(63.34) | 88(36.66) | 240(38.27) |
| | >5cm | 17(54.8) | 14(45.2) | 31 (4.95) |

| | | | | |
|---|---|---|---|---|
| Number of Positive node | <2 | 284(75.53) | 92(24.47) | 376(59.97) |
| | >=2 | 174(69.32) | 77(30.68) | 251(40.03) |
| Treatment mode | Surgery associated with radiotherapy [a] | 165(64.45) | 66(25.65) | 256(40.82) |
| | Surgery[b] | 101(72.66) | 38(27.34) | 139(22.18) |
| | others[c] | 191(82.68) | 65(28.13) | 231 (36.8) |
| Type of surgery | Partial mastectomy | 65 (58.56) | 46(41.44) | 111(23.32) |
| | total mastectomy | 86 (76.1) | 27 (23.89) | 113(23.74) |
| | Modified radical mast | 180 (78.6) | 49 (21.4) | 229(48.11) |
| | Axillary node dissection | 14(60.86) | 9(39.13) | 23(4.83) |
| Chemotherapy | No | 67(72.8) | 25(27.2) | 92 (14.7) |
| | Yes | 391 (73.1) | 144(26.9) | 535(85.3) |
| Endocrine therapy | No | 137(62.27) | 83(37.72) | 220(35.08) |
| | Yes | 321(78.86) | 86(21.13) | 407(64.92) |

[a] Surgery associated with radiotherapy only (or also combined with chemotherapy)

[b] Surgery only (or also combined with chemotherapy) ; [c] Radiotherapy and/or chemotherapy and/or surgery therapy.

## 7.3. Survival status of breast cancer patients

The overall mortality rate in the cohort during the 1,712 person-years of observation (PYO) was 9.87 per 100 (95% CI: 8.49- 11.47) person-years follow up. The cumulative incidence of this study was 169(27%) with the confidence interval (95%CI, 23.6-30.3%) of patients were died over six years. However, 458 (73.04%) were censored till the end of the study. Of these, 194(42.27%) were lost to follow up, 132(28.76%) were alive 119(25.9%) was against medical advice and the rest were transfer to other institution at the end of the follow up. This study shows that those patients with advanced stage of diagnosis (III$IV) have nearly 3 time more likely mortality rate as compared with early stage (10.2 Vs 3.5 deaths per 1,000 person -month).

## 7.4. Overall Survival Function of breast cancer patients

In the present study, 627 breast cancer patients were followed up for a total of 72 months, with a median survival time of 56.5(95% CI, 53.46 - 60.83) months. Kaplan-Meier survival estimation showed that overall estimated survival rate after diagnosis of breast cancer was 26.42% (95% CI, 17.09 to 36.67 %) at 72 months of follow up. The estimated cumulative survival was 97.2%, 89.8%, 80.8%, 66.33%, 46.2% and 26.4% at 12, 24, 36, 48, 60 and 72 months respectively **(Figure 2)**. One can also see on the Kaplan Meir survival curve for time to death of breast cancer patients, the probability of survival decreases as the follow-up time increases. This study found that the highest rate of mortality was occurred between 40 months and 60 months of breast cancer diagnosis.

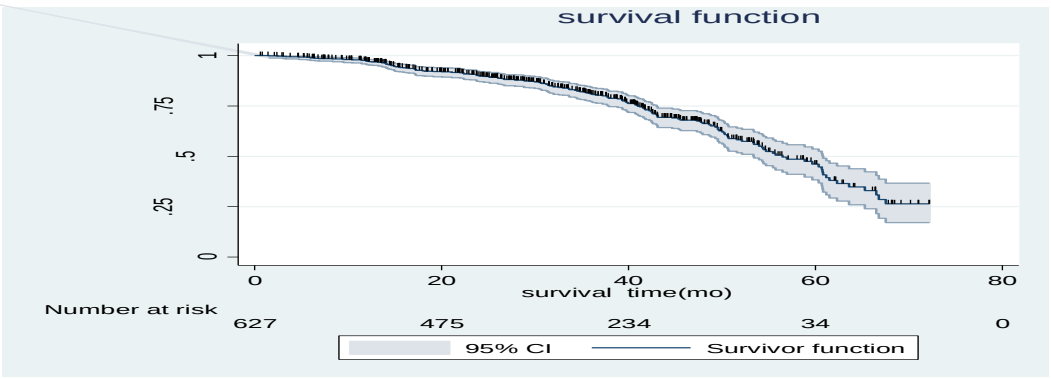


Figure 3:-Overall Kaplan-Meier estimation of survival functions of patients on breast cancer diagnosis at black lion specialized Hospital, Addis Ababa, Ethiopia, from January 1st 2012 to December 31st 2017.

## 7.5. Survival function among different groups of Breast cancer patients

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. In this study, the test statistics showed that there is a significant difference in survival function for different categorical variables. Accordingly, the Kaplan-Meier analysis indicated significant evidence of differences in survival times. It is found that the median survival time for those who had clinical stage I, II or III at baseline had a longer survival time than those in advanced clinical stage (IV) (45.6 months, 95% :41.04- 50.57) this difference was statistically significant with p-value < 0.000. The median survival time for those who have negative lymph node status had a longer survival time was (63.6month, 95%CI: 60.67- .) than those who had positive lymph node at baseline (47.34months, 95% CI: 41.2-49.7).This difference was statistically significant with (p-value = 0.000).

Among 189(30.14 %) cases diagnosed in early stage (I&II), cumulative survival was 56.65% (95%CI: 35.94-72.94%), while, those cases diagnosed at advanced stage (III&IV), 438(69.86%) had a survival rate of 18.49% (95%CI: 10.03-28.98%). Which shows Breast cancer mortality was correlated to the stage at diagnosis and testing equality among the groups with p value of 0.000. A 6-year survival for histological types indicated that, there was a significant difference in survival rates of 20.2% (95%CI,10.82-30%) for those diagnosed with IDC (invasive ductal carcinoma) as compared to other breast cancer types 43.26%(22.39-62.56) (**see below table and figure**).

Table 3:-Survival time, cumulative survival probability, significance and log rank test for the study population according to different characteristics of patients during 6-year of follow-up (Kaplan-Meier method) of breast cancer patients at, black lion specialized hospital, Ethiopia from January 1st 2012 to December 31st 2017 (n=627)

| Covariate | Survival time, mo, (95% CI) | | Overall 6-year survival (%) | Log rank test (p–value) |
|---|---|---|---|---|
| | Mean (95% CI) | Median(95%CI) | | |
| Residence | | | | |
| Urban | 55.6( 52.8-58.30) | 59.7(54.47-..) | 36.57 | |
| Rural | 49.2(46.25-52.2) | 50.73(49.3 -60.67) | 17.26 | (8.83) * |
| Menopause status | | | | |
| Premenopausal | 53.4(50.88- 55.8) | 60.7(53.47- 63.63) | 28.56 | 0.63 |
| Postmenopausal | 50.97( 47.3- 54.64) | 54.5(48.64-58.84) | 19.67 | |
| comorbidity | | | | |
| No | 56.86(54.26-59.45) | 63.64(60.84- .) | 35.62 | (23.18) * |
| Yes | 46.53(43.62- 49.44) | 50.04(45.6-53.37) | 12.89 | |
| Stage | | | | |
| I | 68.96(63.3-74.63) | - - - | 92.86 | |
| II | 58.7( 55.25- 62.18) | 61.54(59.7-..) | 43.56 | (41.46) * |
| III | 50.9(48.3-53.47) | 54.46(50.24-60.67) | 20.18 | |
| IV | 41.48(36.43-46.53) | 45.6(41.04- 50.57) | 16.8 | |
| histology grade | | | | |
| Grade I | 65.56(61.45-69.66) | - - 66.5- | 66.4 | |
| Grade II | 55.82(52.92- 58.72) | 60.74(55.76- 67.54) | 34.6 | (62.38) * |
| Grade III | 44.03(41.36-46.71) | 48.63(42.96 -50.73) | 0 | |
| Deep surgical margin | | | | |
| free | 57.05(54.68-59.43) | 62.3 (59.7- .) | 41.31 | (56.32) * |
| involved | 41.26(37.82- 44.71) | 42.97(39.74-48.34) | 2.93 | |
| Number of involved lymph nodes | | | | |
| <2 | 54.46(51.84-57.08) | 60.74(54.47-66.5) | 30.21 | 3.65 |
| >=2 | 49.77(46.65-52.89) | 53.96(49.6-59.7) | 18.93 | |

| | | | | |
|---|---|---|---|---|
| Tumor size | | | | |
| ≤2.5 | 57.88(55.16-60.61) | 61.53(60.67- …) | 45.65 | (26.42) * |
| 2-5 | 49.04(41.92-56.16) | 50.57(47.96-54.33) | 11.35 | |
| >5 | 46.96(43.96-49.96) | 45.36(41.84-…) | 0 | |
| Metastasis at diagnosis | | | | |
| No | 61.19(58.70-63.68) | 66.5(60.84- .) | 48.5 | (99.9) * |
| Yes | 41.96(39.25- 44.67) | 42.5(40.04- 47.34) | 5.4 | |
| Endocrine therapy | | | | |
| | | | | (40.65) * |
| No | 43.85(41.01-46.69) | 47.97(41.84-51.64) | 6.8 | |
| Yes | 57.37( 54.92-59.81) | 65.3(58.84- .) | 40.58 | |
| Lymph node status | | | | |
| Negative | 57.24(54.86-59.62) | 63.64(60.67- .) | 38.27 | (48.95) * |
| Positive | 42.30(39.39-45.21) | 47.34(41.2-49.7) | 5.1 | |
| Chemotherapy | | | | |
| No | 48.04(43.01-53.08) | 53.47(42.5- | 24.9 | |
| yes | 53.29(51.12-55.47) | 58.84(53.97-61.54) | 27.52 | 2.35 |
| Type of surgery | | | | |
| Partial mastectomy | 47.45(43.34-51.49) | 49.6(43.03-54.34) | 12.6 | |
| Total mastectomy | 54.37(49.67-59.07) | 60.74 (51.64- .) | 39.2 | (19.3) * |
| MRM | 57.69(54.54-60.84) | 62.3 (58.84- .) | 39.4 | |
| Axillary dissection | 37.89(29.27-46.50) | 50.03(14.64- . ) | 0 | |

mo;months,CI;confidence interval ,SE:standard error, MRM;modified radical mastectomy,

∗ indicates that the variables have significantly difference in survival among groups at 95% level of significant ($P < 0.05$).

The mean survival time for those who had clinical stage I, II or III at baseline had a longer survival time than those in advance clinical stage (IV) (41.5 months, 95% CI:36.42-46.53) this difference was statistically significant with p-value < 0.000 (Figure 4).

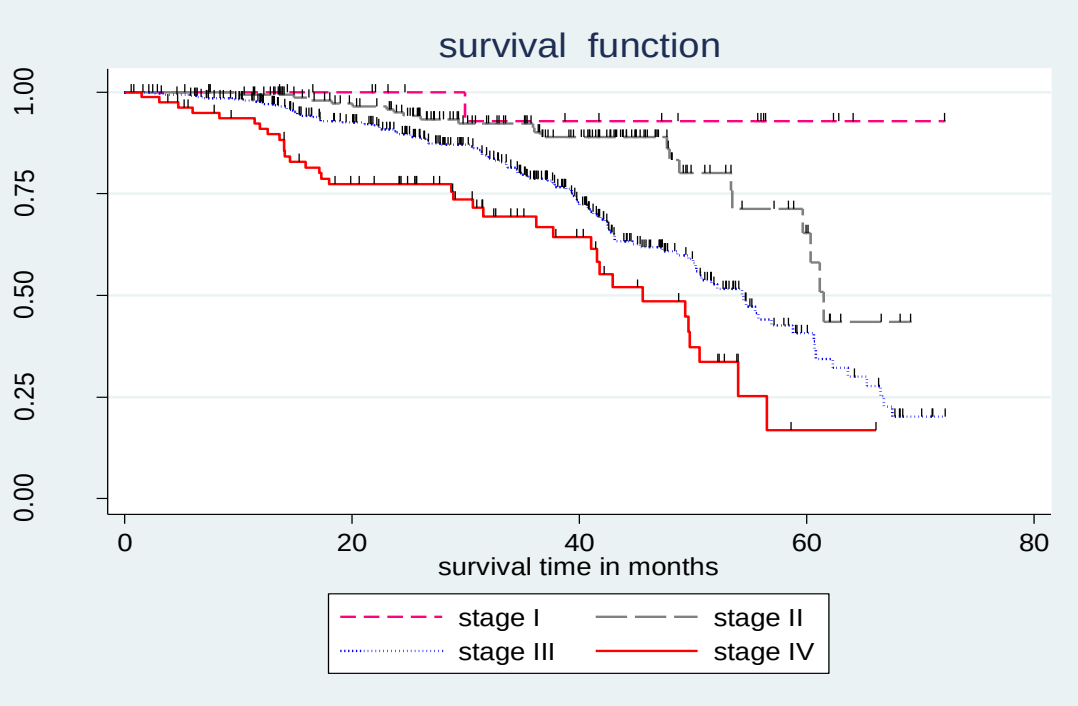


Figure 4:-The Kaplan-Meier survival curves compare survival time of breast cancer patients with different categories of baseline clinical stage in black lion specialized hospital, Addis Ababa ,Ethiopia from January 1st 2012 to December 31st 2017.

The Kaplan-Meier graph shows that mean survival time for those who have taken endocrine therapy was (57.4 months, 95% CI: 54.92-59.81), which is higher than the mean survival time of individuals who have not took endocrine therapy (43.8 months, 95% CI: 41.01-46.69). This difference was statistically significant with p-value = 0.000(Figure 5)

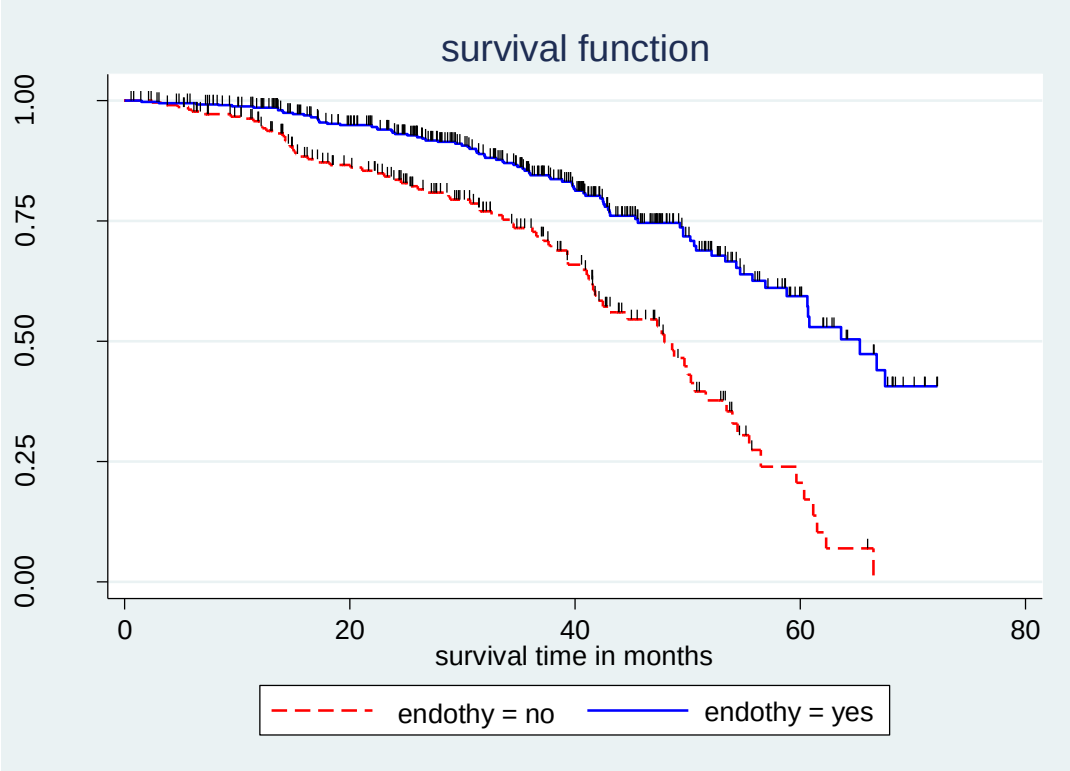


Figure 5:-The Kaplan-Meier survival curves compare survival time of breast cancer diagnosis with different categories of baseline endocrine therapy in black lion specialized hospital, Addis Ababa, Ethiopia from January 1st 2012 to December 31st 2017.

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Regarding with histologic grade the mean survival time for those who had histology grade I, and Grade II at baseline had a longer survival time than those in advance histology grade III (44.03 months, 95% CI:41.36-46.71) this difference was statistically significant with p-value < 0.000 (Figure 6).

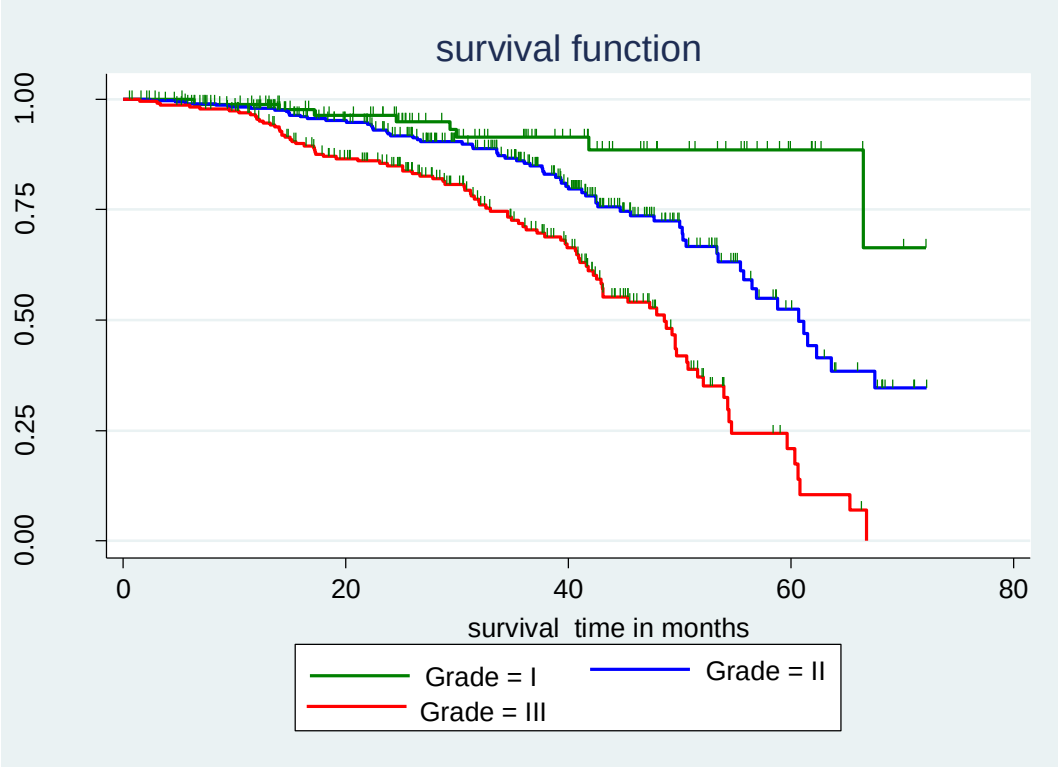


Figure 6:-Kaplan-Meier survival estimation of time to death in breast cancer patient by base line histology grade in black lion specialized hospital, Addis Ababa, Ethiopia from January 1st 2012 to December 31st 2017.

The graph below shows that those who had no metastasis at the time of diagnosis have better mean survival time which is (61.2 months,95% CI: 58.70- 63.68) than those who had metastasis at the baseline (41.9 months, 95% CI:39.25 - 44.67),this difference was statistically significant with p-value < 0.000 (Figure 7)

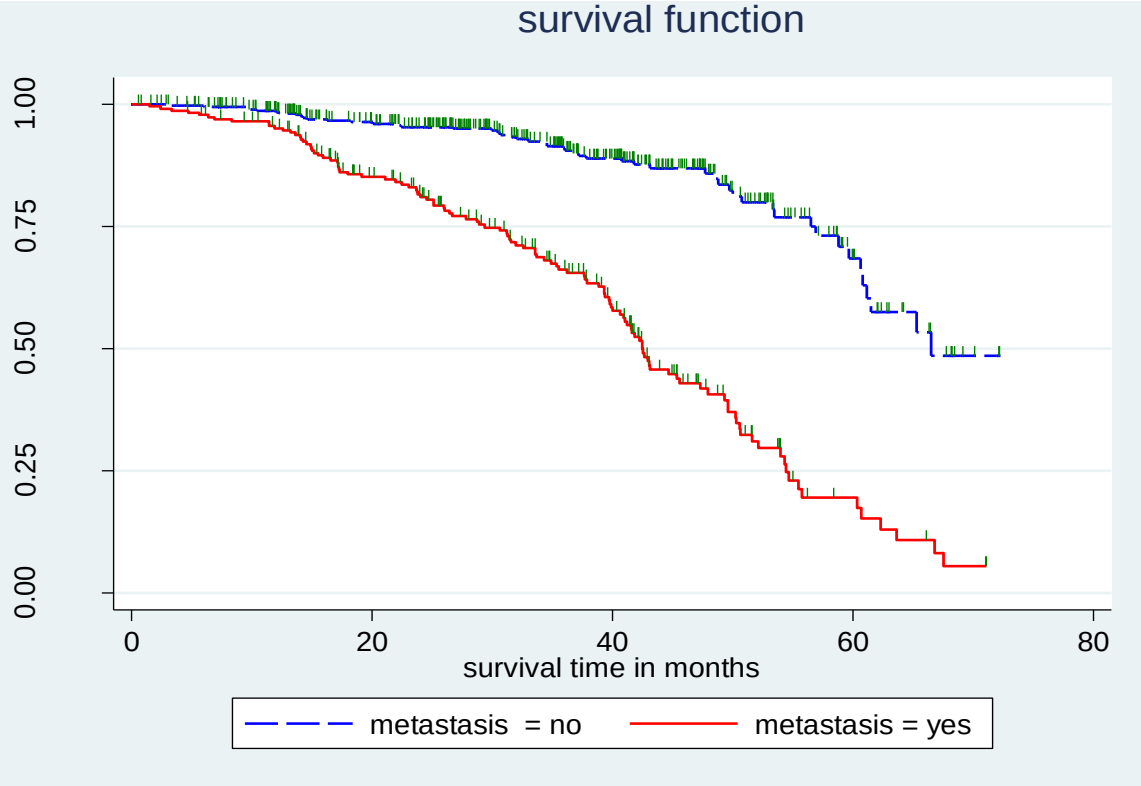


Figure 7:-Kaplan-Meier survival estimation of time to death in breast cancer patient by base line histology grade in black lion specialized hospital, Addis Ababa, Ethiopia from January1st 2012 to December 31st 2017.

The Kaplan–Meier graph along with log rank test shows that mean survival time for those who have live in urban residence had a longer survival time (55.6months, 95% CI: 52.8-58.30) than who had live in rural residence (49.1months, 95% CI: 46.25-52.2).This difference was statistically significant with p-value = 0.000(Figure 8)

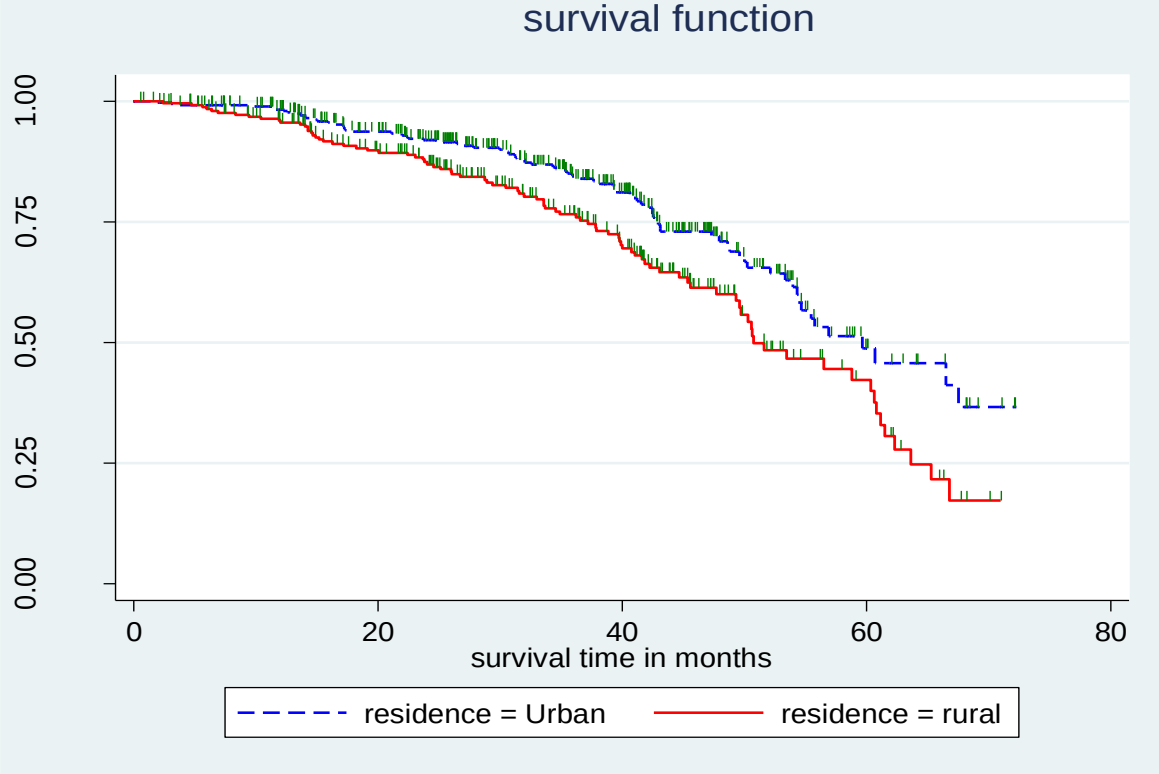


Figure 8:-The Kaplan-Meier survival curves compare survival time of breast cancer diagnosis women with different categories of baseline residential status in black lion specialized hospital, Addis Ababa, Ethiopia from January 1st 2012 to December 31st 2017.

Those who had no preexisting medical disorder at a time of breast cancer diagnosis had a longer mean survival time (56.8months, 95% CI: 54.26 - 59.45) than who had comorbidity. This difference was statistically significant with p-value = 0.000(Figure 9)

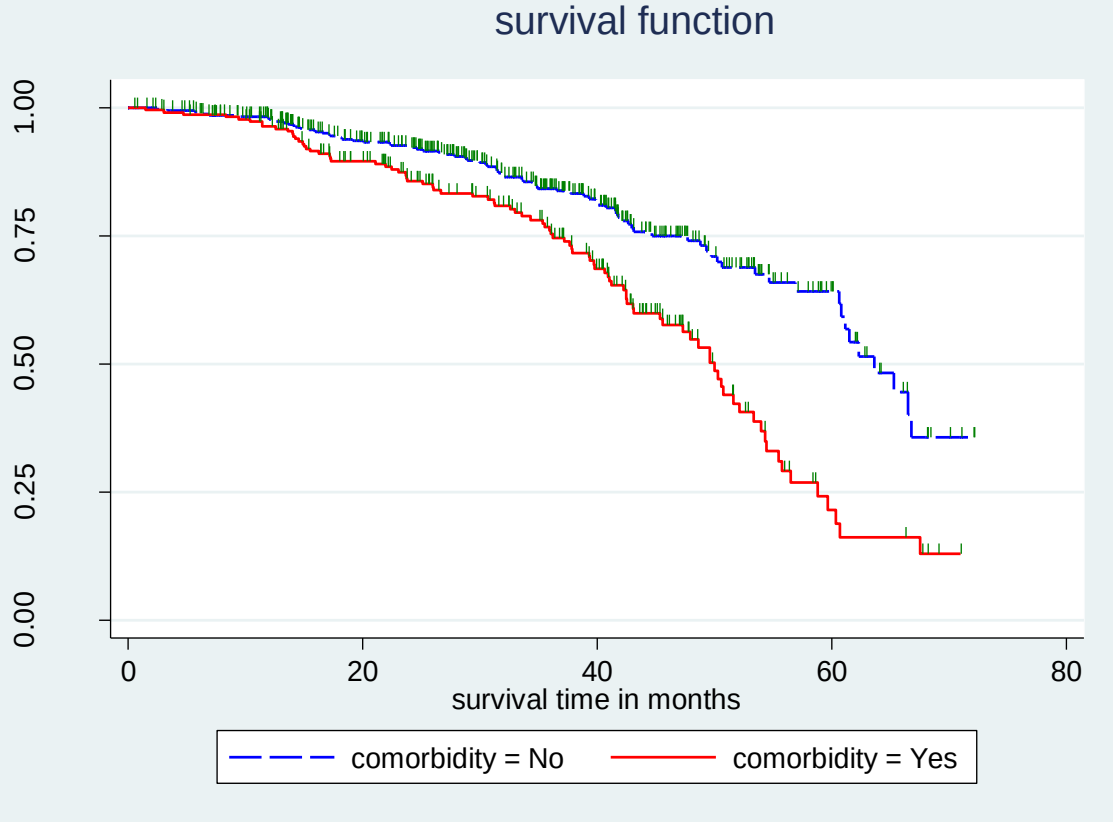


Figure 9:-The Kaplan-Meier survival curves compare survival time of breast cancer diagnosis women with different categories of baseline comorbidity in black lion specialized hospital, Addis Ababa, Ethiopia from January 1st 2012 to December 31st 2017.

The mean survival time for those who had surgical margin involvement at a time of breast cancer diagnosis had a shorter survival time (41.2months, 95% CI: 37.82 -44.70) than who had no surgical margin involvement at baseline which is (57.1 months, 95% CI: 54.68-59.43).This difference was statistically significant with p-value < 0.000 (Figure 10)

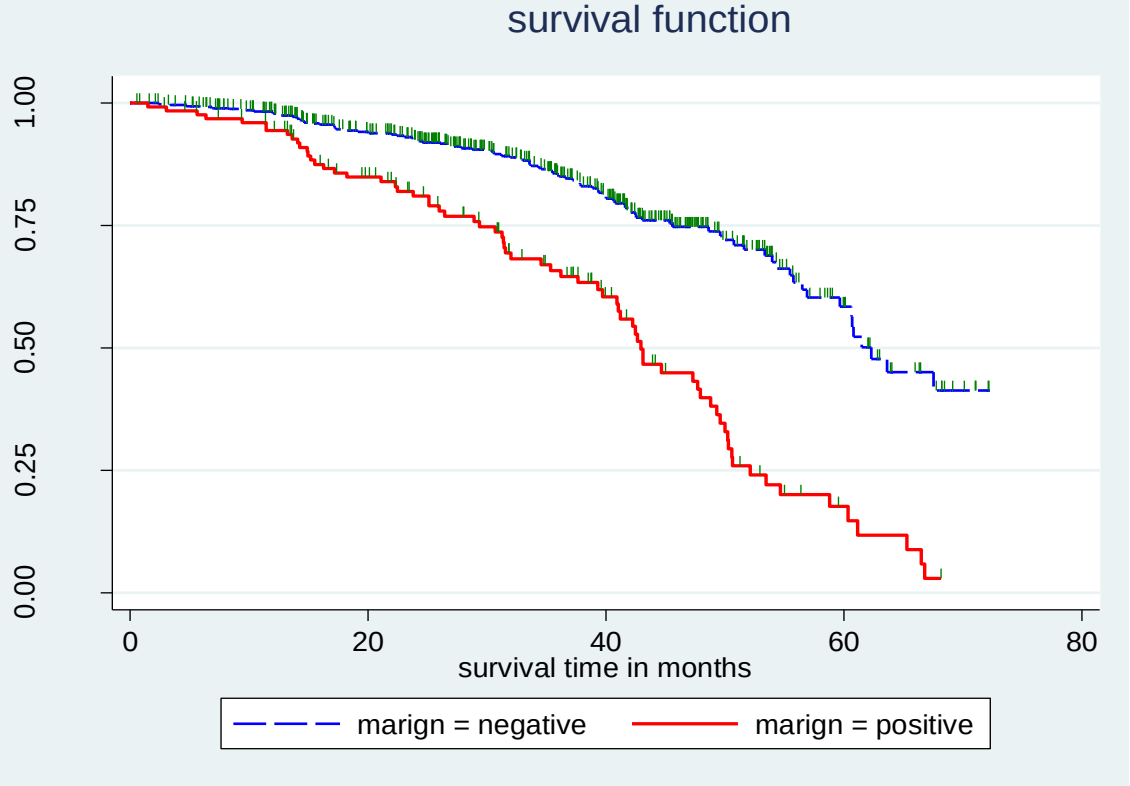


Figure 10:-The Kaplan-Meier survival curves compare survival time of breast cancer diagnosis women with different categories of baseline surgical margin in black lion specialized hospital, Addis Ababa, Ethiopia from January 1st 2012 to December 31st 2017.

## 7.6. Testing overall model fit

This figure shows if the Cox regression model fits the data, these residuals should have a standard censored exponential distribution with hazard ratio. If we comparing the jagged line with the reference line, we observe that the Cox model does fit these data to reasonable. The hazard function follows the 45° line very closely .Hence, the output shows cox–snell residuals were satisfied the overall model fitness test.

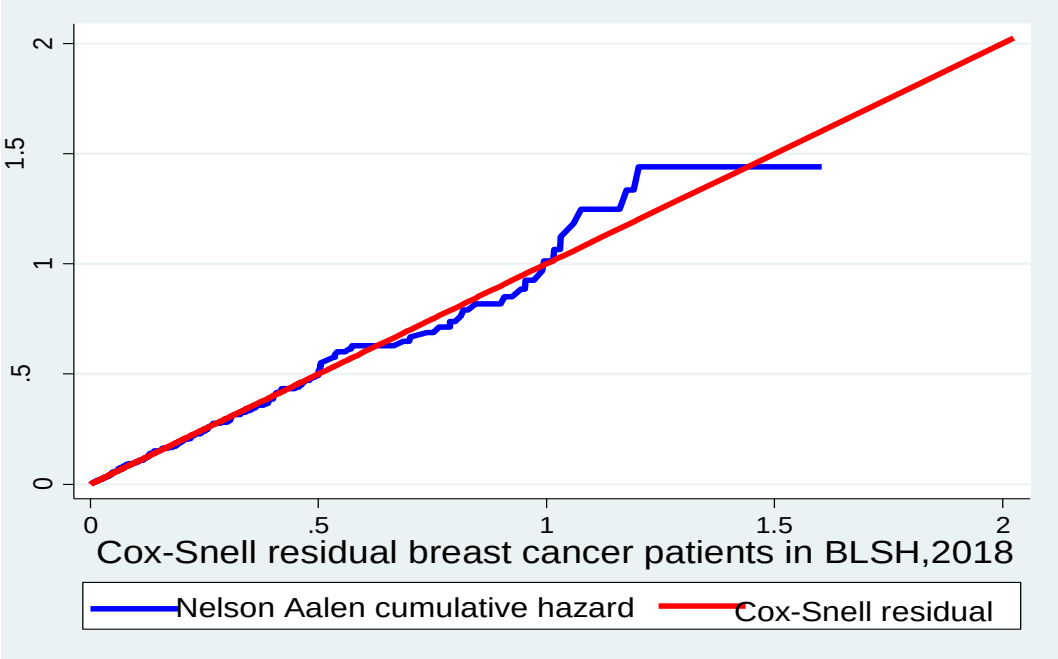


Figure 11 .Cox-Snell residual Nelson -Aalen cumulative hazard graph on breast cancer patients in Black lion specialized hospital, Addis Ababa, Ethiopia, January 1st 2012 to December 31st 2017.

## 7.7. Predictors of mortality

In bivariable cox proportional Hazard regression model, age, marital status, place of residence, histology grade ,stage, surgical margin, comorbidity, tumor size, metastasis at diagnosis ,histology type, lymph node status, type of surgery and endocrine therapy were all associated with survival status (P <0.05).

In multivariate Cox regression analysis those variables with p-value <0.25 in the bivariate analysis and non-collinear independent variables were included. In multivariable cox proportional hazards model, seven variables were associated with breast cancer mortality. The result of multivariable analysis revealed that women with advanced clinical stage (III and IV) were 1.86 times more likely to die as compared to those with early clinical stage (I and II) (AHR : 1.86, 95%CI: 1.127- 3.080). Those women whose surgical margin involved at baseline were 3.13 times more likely to die as compared to those women whose surgical margin was not involved (AHR: 3.13, 95% CI: 2.140- 4.573).

Patients having positive lymph node status were 1.83 times more likely to die as compared to those having negative lymph node at time of diagnosis (AHR: 1.83, 95% CI:1.217- 2.736). women those who are being histologic grade III at the beginning of breast cancer diagnosis were 3.12 times more likely to die as compared to those who are grade I (AHR: 3.12, 95% CI:1.16-8.39). Furthermore, women who are taken endocrine therapy during the six year follow up time were reduced mortality by 33% compared to those who are not taken endocrine therapy (AHR: 0.67, 95% CI: 0.451- 0.989).

Table 4:-Results of the bivariable and multivariable cox regression analysis of breast cancer patients at black lion specialized hospital, Addis Ababa, Ethiopia, January 1st 2012 to December 31st 2017 (n=627).

| Characteristics | Bivariable cHR (95% CI) | Multivariable aHR (95% CI) |
|---|---|---|
| Age | | |
| <40 | 1 | 1 |
| 40-49 | 1.45(1.010-2.089)* | 1.21(.766- 1.898) |
| 50-59 | 1.21(0.761-1.919) | 0.88(0.468- 1.660) |
| 60-69 | 1.84(1.080-3.141)* | 1.62(0.766- 3.447) |
| >70 | 2.56(1.221- 5.376)* | 2.46(0.822- 7.371) |
| Place of residence | | |
| Urban | 1 | 1 |
| Rural | 1.57(1.164-2.130)* | 1.48(0.999-2.195) |
| Marital status | | |
| Married | 1 | 1 |
| Single | 1.07(.708- 1.629) | 0.95(0.551- 1.638) |
| Widowed | 1.77(1.224- 2.568)* | 0.69(0.395- 1.224) |
| Divorced | 1.34(0.826- 2.363) | 0.67(0.318 -1.422) |
| comorbidity | | |
| no | 1 | 1 |
| yes | 2.07(1.530- 2.808)* | 1.49(0.980- 2.290) |
| Stage of breast cancer | | |
| Early (I&II) | 1 | 1 |
| Advanced (III&IV) | 3.11(2.01-4.84)* | 1.86(1.127-3.080)** |
| Histology grade | | |
| Grade I | 1 | 1 |
| Grade II | 2.92(1.40-6.09)* | 1.73(0.67-4.53) |
| Grade III | 6.79(3.28-14.06)* | 3.12(1.16-8.36)** |
| Histology type | | |
| Invasive Ductal | 1.87(1.298-2.714)* | 1.04(0.644- 1.697) |
| Others | 1 | 1 |
| Surgical margin involved | | |
| No | 1 | 1 |
| Yes | 3.06(2.252-4.168)* | 3.13(2.140- 4.573)** |
| No of involved lymph node | | |
| <2 | 1 | 1 |
| >=2 | 1.34(0.991-1.822) | 0 .79(0.517- 1.205) |
| Lymph node status | | |
| Negative | 1 | 1 |
| positive | 1.61(1.396-1.848)* | 1.83(1.217- 2.736)** |

| | | |
|---|---|---|
| Tumor size | | |
| ≤2.5 | 1 | 1 |
| 2-5 | 2.19(1.593-3.021)* | 1.15(0.736- 1.832) |
| >5 | 2.08(1.172-3.717)* | 2.31(0.891-4.123) |
| Lung metastasis | | |
| No | 1 | 1 |
| yes | 1.27(0.880- 1.833) | 1.36(0.936- 1.969) |
| Liver metastasis | | |
| No | 1 | 1 |
| yes | 1.38(0.95-2.006) | 1.25(0.850- 1.838) |
| Type of surgery | | |
| Partial mastectomy | 1 | 1 |
| Simple (total) mastectomy | 0.61(0.378- 0 .986) | 0 .68(0.413- 1.134) |
| MRM | 0.48(0.318-0.714)* | 0.45(0.280- 0 .690)** |
| Axillary node dissection | 1.51(0.735-3.084) | 1.25(0.593- 2.660) |
| Radiotherapy | | |
| No | 1 | 1 |
| yes | 0.79(0.586-1.074) | 0.95(0.654- 1.381) |
| Chemotherapy | | |
| No | 1 | 1 |
| yes | 0.72(0.467-1.099) | 0.27(0.130-0.565)** |
| Hormone therapy | | |
| No | 1 | 1 |
| yes | 0.38(0.281-0.519)* | 0.67(0.451-0.989)** |

CI; confidence interval, aHR; adjusted Hazard ratio, cHR: crude hazard ratio, MRM; modified radical mastectomy, *indicates that the variables significantly associated with the outcome at bivariable analysis 95% level of significant ($P < 0.05$). ** indicates that the variables significantly associated with the outcome at multivariable analysis 95% level of significant ($P < 0.05$).

## 7.8. Testing proportional hazard assumption

A Cox regression model was used to examine the effects of sociodemographic, clinical and treatment characteristics of patients on time to death. The following variables were included in the model as predictors: place of residence, age group, and marital status, and menopausal status, stage at diagnosis, histology grade, primary treatment, and hormone therapy. A goodness-of-fit (GOF) test was conducted to assess the proportional hazard (PH) assumptions of the Cox model for given predictor variables (Table). The findings indicated that all variable included in the model were satisfy PH assumptions (p-value>0.05).

Table 5:-Goodness-of-fit test assessing proportional hazards Assumption

| Predictors | rho* | Chi-square test | df** | p-value |
|---|---|---|---|---|
| Place of residence | 0.00841 | 0.01 | 1 | 0.9327 |
| Marital status | -0.04650 | 0.26 | 1 | 0.6121 |
| Menopausal status | -0.02790 | 0.08 | 1 | 0.7716 |
| Comorbidity | 0.04656 | 0.25 | 1 | 0.6180 |
| Histology grade | 0.06188 | 0.53 | 1 | 0.4672 |
| Surgical margin | 0.05037 | 0.24 | 1 | 0.6228 |
| Lymph node status | 0.01964 | 0.04 | 1 | 0.834 |
| Lung metastasis | -0.04802 | 0.23 | 1 | 0.6334 |
| Liver metastasis | 0.18526 | 3.77 | 1 | 0.0522 |
| Radiotherapy | 0.02415 | 0.07 | 1 | 0.7970 |
| Chemotherapy | -0.06344 | 0.45 | 1 | 0.501 |
| Type of surgery | -0.02748 | 0.09 | 1 | 0.7678 |
| Endocrine therapy | 0.08963 | 0.88 | 1 | 0.3478 |
| Age at diagnosis | 0.03969 | 0.18 | 1 | 0.6671 |
| Tumor size | 0.07322 | 0.52 | 1 | 0.4711 |
| No of lymph involved | -0.10249 | 1.05 | 1 | 0.3047 |
| Stage at diagnosis | 0.05755 | 0.32 | 1 | 0.5692 |
| Histology type | -0.03853 | 0.15 | 1 | 0.7012 |
| Global test | | 9.86 | 18 | 0.936 |

**The correlation coefficient between the residuals and time.*
***Degree of freedom.*

## 8. Discussion

This study aimed to asses' survival status and predictors of mortality among breast cancer patients. At the end of follow up, about 169 patients were dead and 458 patients were censored, resulting in a total cumulative incidence of death was 27% over six years and a mortality rate of 9.8 per 100 person-years. This finding is in line with WHO breast cancer mortality profile in Ethiopia which is 24.4% [20], Nigeria 28%[28].However, the total number of deaths that occurred in this study was lower than other studies conducted in Ghana showed 38.16% [22], ,Hawaii 37.4% [25]. Although there were also studies which reported lower findings with this study in Uganda (23 %) [29]. The discrepancy of results, which has been seen among studies, might be difference in sample size .Other, possible explanation might be the difference in the study period as there were changes in treatment modality and also might be continuity of patients care through time. Moreover, some of the findings from African countries has estimated mortality of maximum 5 years follow up which might have estimated low death proportion than the present finding.

In the current study, the overall mortality rate of breast cancer patients during 72 months follow up was 9.8/100 women- years. This finding is much higher than what was reported in a study in brazil [26] , where age-standardized breast cancer mortality rate within 6 year follow up period of 431.8 /100 000 women-years was found. The observed difference in mortality rates may be due to, the fact that more advanced stage (III$IV) breast cancer were presented in our finding. Other possible explanation could be methodology difference; they have been used ecological analysis.

In this 6-year retrospective follow up study, the overall survival rates at 1, 3, and 5 years were, 97.2%, 80.8%, and 46.2% respectively. This finding is consistent with other previous studies which have been conducted in Malaysia (70.8%, 56.9% and 49.4%) [30] and Ghana, (47.9%)[22]. However, this finding is higher than those in other African countries in Tanzania (21.8%)[35] and Cameroon (30%) [32] at 5 years and even lower than previous results in Uganda (51.8 %)[29], and Vietnam, (94%, 83% and 74%) [4].This ,figure is still lower when compared with that of studies of high income countries such as Northwest Iran (96%, 86%, and 81%), Germany( 83% ),and the Qidong (83.61%,67.53%,and58.75%)respectively[31, 36, 39]. Similarly, the overall cumulative 6 years estimated survival rate of the current study was 26.42%

(95% CI: 17.09-36.67 %) at 72 months of follow up. This, finding is lower than the study done in Qidong (56.04%) [39].

This gap might be due to several reasons. However, the difference in breast cancer survival rate among countries and areas of the same country exist and are not easy to interpret. This perhaps could be due to advanced stage at diagnosis in ours (69.5%), however 52.3% in Ghana, 27.6% Vietnam, 67.8% in Cameroon, lack of early screening programs, limited treatment facilities, and financial problems. Other explanation could be the facilities to treat cancer are located in the capital city of the country; hence, most cancer patients were referred to the central level this could result delay in diagnosis and treatment. Additional, possible explanation variations in survival could be due to different methodologies applied in each of the studies but also to different sample compositions regarding stage, age, and other biologic tumor factors, as well as differences in local cancer care. Furthermore, the molecular and genetic differences in breast cancer may also contribute to geographic variations in survival.

In our study, the overall median survival for histologically confirmed breast cancer was 56.5(95% CI, 53.46 - 60.83) months. Our results were higher than the previous studies in which the median survival was 24 months in Cameroon [32], 40 months in Sudan [34].but lower than to the result reported from Malaysia the median survival was 68.1 months [30]. Although, our study showed higher overall median survival than that seen in the Cameroon and Sudan studies, the lower value obtained in comparison with Malaysia is most probably due to shorter period of study in ours. In addition, it could be difference in health seeking behaviour and treatment adherence among those studies.

Overall survival varies according to the stage of breast cancer.In the current study, the overall survival of patients diagnosed with stage I & IV after 6–years was 92.86%, and 16.8% respectively.This finding is in line with the study conducted in Gahanna that reveals a 5-year survival rates for stages I,& IV were, 91.94% and 15.09% respectively[22].Likewise, a study done in Sudan shows patients diagnosed with stage I had better survival and those diagnosed with stage IV had poor survival(100% for stage I, and only 5% for stage IV)[34] .However, this finding is also lower than the study conducted in western amazon Brazil (93.3%, 50% respectively) at stage I and IV respectively[38]. Better survival was observed in patients with early stages of the diseases. This might be reflects that early detection and treatment greatly

improves the survival rate of breast cancer patients. Moreover, it could be concluded that, the high mortality of breast cancer is due to inadequate public information, poor screening, and late presentation of our patients.

In the log rank test it is found that there is a significant difference in survival experience between different baseline characteristic of breast cancer patients. To test the equality of survival curve Kaplan-Meier analysis of survival status showed that the median survival time for those who had clinical stage I, II or III at baseline had a longer survival time than those in advance clinical stage (IV) (45.6 months, 95% :41.04- 50.57) this difference was statistically significant with p-value < 0.000. Similarly, the median survival time for those who have negative lymph node status had a longer survival time was (63.6month, 95%CI: 60.67- ..) than those who had positive lymph node at baseline (47.34months, 95% CI: 41.2-49.7). This finding is in line with study done in African countries [33, 34].

In the present study, lymph node status was found to be an independent predictor of mortality among breast cancer women. Women who had positive lymph node at diagnosis were nearly 2 times higher risk of death as compared to women who had negative lymph node at baseline. This finding is in agreement with different studies conducted in African countries [22, 43],and also in the study done in Iran [42] ,in which lymph node status was an important determinant of survival. Despite being positive lymph node status, as the number of involved lymph nodes increases, so does the relapse rate, while the survival rate decreases. In the current study, histologic grade found to be an independent predictor of mortality. Women who had histologic grade III at diagnosis were nearly 3 times higher risk of death as compared to women who had well differentiated histologic (grade I) at baseline. This finding is in line with other previous studies which have been conducted in Asian countries,[30, 42, 47].

According to the results of this study, those women whose surgical margin involved at baseline was found to be a strong predictor of mortality among breast cancer women. Women who had surgical margin involved at diagnosis were 3.13 times higher risk of death as compared to women who had surgical margin free at time of diagnosis. Most of previous studies also found twice or more risk of mortality in patients with surgical margin involved compared to those with surgical margin free [4, 29, 38], which reflect surgical margin was an important determinant of survival.

Such findings could be explained by the fact that residual disease at the surgical margins could increase the risk of local recurrence and possibly death through the years

As shown by others, we found that advanced clinical stage (III and IV) was found to be a strong marker of mortality among breast cancer women. Women who had clinical stage (III and IV) at diagnosis were nearly 2 times higher risk of death as compared to women who had clinical stage (I$II) at time of diagnosis. This finding is in agreement with several studies conducted in different Africa and Asian countries [4, 29, 31, 47] .Stage is an important predictor of survival from breast cancer, and the most significant influence on patient outcome in the present study.

The result from this study shows patients who had undergone modified radical mastectomy (MRM) was found to be a predictor of prolonged survival and reduced incidence of death AHR, 0.45(0.280- 0 .690).That is women who were operated MRM had 55% more chance of surviving than those who did undergone lumpectomy(breast conserving surgery) at any time. This finding is in contrary with studies done in different Africa and Asian countries [32, 36, 42], which identified breast conserving surgery, have better survival than mastectomy. The difference in survival a mong two groups could be because of advanced stages at presentation and poor infrastructure for treatment of breast cancer have made this mode of surgical treatment more popular in many developing countries including Ethiopia. Scientifically, breast-conserving surgery is usually indicated for early breast cancer in contrast to modified radical mastectomy whose indications also include advanced stage disease. Other possible explanation could be the options for treating a patient with breast cancer depends on the stage of disease.

Unlike most of previous findings [33, 38, 45], chemotherapy was found to be an independent predictors of survival that becomes statistically significant in the cox proportional hazard model. Those women who had receiving chemotherapy was significantly predictor to reduced incidence of death, AHR 0.27 (95%CI: 0.130- 0.565) patients without chemotherapy had 27% more chance of death than that of patients who was treated. However, this finding is in line with study done in France [51] ,which exhibited a 25% reduction in the relative risk of death compared with the untreated group (HR = 0.75 [0.69–0.83], p<0.0001).Generally, our study found a positive effect of chemotherapy on survival for breast cancer patients. Those who had taken chemotherapy, lower the risk of death due to breast cancer. This might be due to patients with advanced stage breast cancer, chemotherapy may be, applied in order to shrink the tumor size and facilitate surgery. In addition, chemotherapy may be, given after surgery in order to reduce the risk of

recurrence arising from residual disease. For patients in our study, the better survival rate was related to patients receiving chemotherapy. Additional studies should be conduct to confirm a positive impact of chemotherapy on survival rate of breast cancer.

The final predictor of survival found in the study was hormone therapy within a 6-year treatment course. This therapy reduced the risk of death among breast cancer patients in the study population. The finding is consistent with previous findings in many studies all over the world [4, 33, 45].Where, hormone therapy was found to have a protective effect for mortality (AHR, 0.67; 95% CI, 0.451- 0.989). The effect of hormone therapy on survival improvement was often mentioned along with the influence of hormone receptors.

# 9. Limitation and Strength of the study

## 9.1. Limitation of the study

This study has some limitations. First, cause specific (relative) survival was not determined due to lack of data on specific cause of death, this may over estimates breast cancer related mortality rate. Second, lack of data on hormone receptors; ER(estrogen receptor),PR(progesterone receptor) and HER2(Human Epidermal Growth Factor Receptor 2) prevented us from analyzing the role of them on survival time. However, several studies reported this as an important determinant, and we were not able to see the effect of treatment adherence on survival. Likewise, information on socioeconomic status, such as occupation and educational level, were not recorded. Selection bias is possibly introduced during secondary data collection because patients with incomplete records were excluded. Moreover, the data were collected over the period January 1$^{st}$ 2012 to December 31$^{th}$ 2014 and do not reflect current utilization of advanced treatment methods and new medications for breast cancer treatment, which could affect the opportunity to improve survival probability in the study population.

## 9.2. Strength of the study

In spite of the above possible limitations, the study has the following strengths: this gives an insight for researchers especially for prospective follow up study, the study was conducted slightly for a longer period, which increases the number of events. Selecting patients from histologically confirmed breast cancer diagnosis has the advantage of providing good-quality data regarding stage, histologic tumor grade, and type. Data were collected by Nurses who were trained on cancer care this has an important role in the quality of the data.

# 10. Conclusion

The overall probability of survival in patient's diagnosis of breast cancer was 27%,at 72 months of follow up, were inferior when compared with those of high and middle income countries. Significant predictors of mortality after diagnosis of breast cancer were; advanced clinical stage, grade III histology, surgical margin involvement, positive lymph node status, In contrast, hormone therapy, modified radical mastectomy and chemotherapy were reduced mortality.

## 11. Recommendation

Based on this study finding, the following recommendations should have been forwarded with each respective bodies:-

**To federal minister of health**

- ✓ Should expand breast cancer early screening programs (breast self-examination, clinical breast exam and mammography) to improve treatment results in breast cancer.
- ✓ Could be strengthen awareness in collaboration with public medias about breast cancer prevention, screening and treatment is crucial.

**To Black lion specialized hospitals**

- ✓ Increasing the availability and accessibility of hormone therapy irrespective of receptor status crucial to improve survival time.
- ✓ Could give special emphasize to those from rural residence and having comorbidity at the time of diagnosis.
- ✓ Enhance treatment using feasible and effective regimens.
- ✓ The healthcare providers could be enhanced the awareness of early sign and symptoms of breast cancer and encouraging women to seek clinical help is an important activity.

**To Future researchers**

- ✓ Further studies on survival status among breast cancer patients that can address the limitations of this study and create strategies to improve completeness by use of prospective design.
- ✓ Further prospective follow up study could be conducted by incorporating important predictors of mortality like financial problems, treatment adherence, societal and health system related factors.

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## 13. Appendix

**Annex 1: information sheet English version**

**Title of the Research proposal:** Survival status and predictor of mortality among Breast cancer patients in Black Lion Specialized Hospital Adult Oncology Unit, Addis Ababa, Ethiopia,2018.

**Name of Investigator**: wondimeneh shibabaw (BSC)

**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 Black Lion Specialized Hospital, 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 Predictors of mortality among breast cancer patients on follow up at black lion specialized hospital adult oncology unit,Addis Ababa, Ethiopia, 2018.

**Procedure:** In order to achieve the above objective, information, which is necessary for the study, was taken from breast cancer 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 1$^{st}$ 2012 to December 31th 2014 was selected and followed up-to Dec 31, 2017 and a review of the required information from the records were 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 will be conducted by taking appropriate information from medical chart, it will not inflict any harm on the patients. The name or any other identifying information will not be recorded on the questionnaire and all information taken from the chart will be kept strictly confidential and in a safe place. The information extracted will be kept

secured by locked in to locker by key. After the data will be entered in to the computer by password. The information retrieved will only be used for the study purpose.

**Benefits:** the research has no direct benefit for those whose document/ record is 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 is a benefit for clients in the program of getting appropriate care and treatment services for the breast cancer patients. Of all, the research work has a paramount direct benefit for health care planners and managers, especially for those on breast cancer program planning and management**.**

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

Person to contact: This research project will be 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.

1.Tefera Mulugeta (BSCN, MSCN), PHD fellow: Addis Ababa University, college of health sciences, school of nursing and midwifery. Tel:

2. Habtamu Abera (RN, BSCN, MSCN), Assistance Professor: Addis Ababa University, college of health sciences, school of nursing and midwifery. Tel:

3.Wondimeneh shibabaw (BSCN): Debre Birhan university .Tel:0928432201, **E-mail:** wshibabaw2015@gmail.com.

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.

**Annex -II**

The American Joint Committee on Cancer TNM classification scheme for staging breast cancers

Tumor (T) Classification:

Tis: Non-invasive tumor (in situ)

T0: No evidence of primary tumor

T1: Invasive tumor, 2 cm or smaller

T2: Invasive tumor, between 2 and 5 cm

T3: Invasive tumor, larger than 5 cm

T4: Invasive tumor of any size, attached to, or invading, surrounding tissues, including inflammatory carcinoma

Lymph Node (N) Classification:

N0: No spread to lymph nodes detected, negative lymph nodes

N1: Spread to lymph nodes in underarm, positive lymph nodes

N2: Lymph nodes in underarm attached to each other or surrounding tissues

N3: Spread to lymph nodes beside breast bone

Metastasis (M) Classification:

M0: No spread detected

M1: Spread to lymph nodes above collarbone, or spread to other parts of the body

This information is collapsed into a few categories called summary stages. These „summary stages‟ can be determined clinically or pathologically or both.

Stage 0: Tis, N0, M0

Stage I: T1, N0, M0 6

Stage IIA: T0, N1, M0

T1, N1, M0

T2, N0, M0

Stage IIB: T2, N1, M0

T3, N0, M0

Stage IIIA: T0-3, N2, M0

T3, N1-2, M0

Stage IIIB: T any, N3, M0

T4, N0-2, M0

Stage IIIC: T any, N3, M0

Stage IV: T any, N any, M1

**Annex -III**

The Charlson comorbidity index. Each condition is assigned with a score of 1, 2, 3 or 6 depending on the risk of dying associated with this condition**.**

**Conditions**

Acute Myocardial Infarction

Congestive Heart Failure

Peripheral Vascular Disease

Cerebrovascular Disease

Dementia

Chronic Obstructive Pulmonary Disease

or other Respiratory diseases

Rheumatic-like Diseases

Ulcers of the Digestive System

Liver Disease – Mild

Diabetes - No Chronic Complications

Diabetes with Chronic Complications

Hemiplegia or Paraplegia

Renal (Kidney) Disease

Cancer (No secondary found)

Liver Disease - Moderate or Severe

Cancer (Metastatic - secondary)

HIV / AIDS

Annexes IV: Data extraction form of English version

Table 6:-Data extraction form for the Assessment of survival status and predictors of mortality among Breast cancer patients at Black Lion Specialized Hospital Adult Oncology Unit, Addis Ababa, Ethiopia ,January 1st 2012-december31th 2017.

| | | | |
|---|---|---|---|
| **Part I: Socio demographic characteristics** | | | |
| 1 | Identification number | ---------- | |
| 2 | Patient Age at diagnosis | ----------year | |
| 3 | Place of residence | 1.Urban(regional town, zonal town, district town)<br>2. Rural | |
| 4 | Marital status | 1.Single<br>2. Married<br>3.Widowed<br>4.Divorced | |
| 5 | Level of Education | 1. No formal Education<br>2.Primary school<br>3. Secondary education<br>4. College<br>5. University<br>6.Other specify _____ | |

| | | | |
|---|---|---|---|
| **6** | Menopausal status | 1.Premenopausal<br>2. Postmenopausal | |

| | | | |
|---|---|---|---|
| **7** | Pre-existing medical diseases at time of diagnosis (For a listing of condition , please refer to Annex III ) | 1. No<br>2. Yes<br>3. Unknown | |
| **Part two:- clinical and histopathological variable** | | | |
| **1** | Date of breast cancer diagnosis | ---------/----------/-------- | |
| **2** | Laterality | 1.left<br>2.right<br>3.both side | |
| **3** | Basis of diagnosis | 1.clinically(physical exam, radiology)<br>2.cytology<br>3.histology of primary<br>4.histology of metastasis<br>5.unkown | |
| **4** | Primary site of breast cancer | 1.nipple<br>2.upper inner quadrant<br>3.lower inner quadrant<br>4.upper outer quadrant<br>5.lower outer quadrant<br>6.axillary tail of breast<br>7.overlapping lesion and midline | |
| **5** | Stage of cancer at diagnosis | 1) I<br>2) II<br>3) III<br>4) IV | |
| **6** | Histological grades of breast cancer | 1. well differentiated<br>2. moderately differentiated | |

| | | | |
|---|---|---|---|
| | | 3. poorly differentiated<br>4. undifferentiated<br>5.not determined | |
| 7 | Histology type of breast cancer | If Noninvasive carcinoma<br>1.Ductal carcinoma insitu<br>2.Lobular carcinoma insitu<br>If Invasive carcinoma<br>1.Ductal<br>2.Lobular<br>3.Medullar | |
| **8** | Deep surgical margin | 1. Involved<br>2. Free/negative/ | |
| **9** | Number of lymph nodes involved | --------- | |
| **10** | Lymph Node status | 1.positive<br>2.negative<br>9.missing | |
| 11 | Tumor size in centimeter | ---------- | |
| 12 | cancer metastases at diagnosis | 1.none<br>2.distance lymph node positive<br>3.distance metastasis not lymph node<br>4.contiguous extension from lymph to skin<br>5.distance lymph node and other metastases | |
| 13 | Cancer metastases at diagnosis to bone | 1.yes<br>2. no | |

| | | | |
|---|---|---|---|
| 14 | Cancer metastases at diagnosis to brain | 1.yes<br>2. no | |
| 15 | Cancer metastases at diagnosis to lung | 1.yes<br>2. no | |
| 16 | Cancer metastases at diagnosis to liver | 1.yes<br>2. no | |
| 17 | Estrogen receptor: | 1. Negative<br>2. Positive<br>3. Not stated | |
| 18 | Progesterone receptor: | 1. Negative<br>2. Positive<br>3.Not stated | |
| 19 | Human epidermal growth factor receptor: | 1. Negative<br>2. Positive<br>3. Not stated | |
| **Part three:- Treatment related variable** | | | |
| 1 | Date of starting treatment | ----------year | |
| 2 | The primary treatment initiated | 1. Radiotherapy _____<br>2. Chemotherapy_____<br>3. Radiotherapy & Chemotherapy _____<br>4.Surgery,Radiotherapy and chemotherapy_____<br>5 Palliative care | |
| 3 | If chemotherapy | 1. Regimen<br>2. how many cycles | |

| | | | |
|---|---|---|---|
| | | 3. Record total dose (or average) given for each cycle, by individual drug (units). | |
| 4 | If radiotherapy total dose of irradiation<br><br>Number of rounds | ----------<br><br>---------- | |
| 5 | If surgery was done: type of surgery | **1.** Partial mastectomy (lumpectomy or quadrantectomy)<br>**2.** Simple (total) mastectomy<br>**3.** Modified radical mastectomy<br>**4.** Radical mastectomy<br>**5.** Axillary node dissection<br>**6.** Other surgery---------- | |
| 6 | Was she on endocrine therapy? | 1. yes<br>2. no | |
| **7** | If yes please mention | 1.drug type ----------<br>2. starting date _____<br>3.total months of use---------- | |
| 8 | Status of the patient during last contact | 1.death<br>2.censored (alive , lost follow up, transfer to and against medical advice) | |
| 9 | If dead, lost to follow up, transfer to or alive when last date of contact | ____/____/____ | |
| | Data abstractor name<br>Abstraction date | ----------<br>----------/-------/-------- | |