Survival Time and Predictors of Breast Cancer Treatment Outcome at St. Paul's Hospital Millennium Medical College, Oncology Unit, Addis Ababa, Ethiopia, 2024

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ABBREVIATIONS

AARHB-	Addis Ababa Regional Health Bureau
AHR-	Adjusted Hazard Ratio
BC-	Breast Cancer
BMI-	Body Mass Index
CI-	Confidence Interval
DALYs -	Disability Adjusted Life Years
DLICs-	Developing and low-income Countries
ETB-	Ethiopian Birr
HDI-	Human Development Index
HER2-	Human epidermal growth factor receptor 2
HIV-	Human Immunodeficiency Virus
IRB-	Institutional Review Board
KM-	Kaplan–Meier
LMIC-	Low-middle Income Countries
LN-	Lymph Node/s
MFS-	Metastasis Free Survival
MOH-	Ministry of Health
ROCs -	Reproductive Organ Cancers
RR-	Relative Risk
SPHMMC-	St. Paul's Hospital Millennium Medical College
SPSS-	Statistical Package for Social Sciences
SSS-	Sub-Saharan Africa
St. Paul's-	Saint Paul's
US-	United States
WLWH-	Women Living with HIV
WHO-	World Health Organization

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SUMMARY

Background: The incidence and mortality rate of breast cancer is highest in Africa, especially in the Sub-Saharan African countries. Despite significant advances in early detection, treatment technologies, and targeted therapies, breast cancer treatment outcomes remain poor. The median survival time was 38.3 months. Different socioeconomic and cultural settings, budgetary constraints, and limited resources have all been demonstrated to affect treatment outcomes. It is especially concerning in low and middle-income countries where there is increasing trend of prevalence and mortality. Although some studies have been conducted, they are not recent and hence do not reflect the current utilization of treatment methods, they had small sample sizes and were conducted in different areas and set up. Thus, the study will fill these gaps and aim to assess the survival time and predictors of breast cancer treatment outcome.

Objective: The main objective of this study is to assess the survival time and predictors of breast cancer treatment outcome at St. Paul's Hospital Millennium Medical College, Oncology Unit, Addis Ababa, Ethiopia, 2024.

Methods: A retrospective cohort study was conducted among 307 female adult patients with breast cancer undergoing treatment from January 2019 to December 2023 in the study setting. They were selected by simple random sampling using computer-generated method. A pre-tested data extraction tool was used to collect data from the patient medical records. Data was coded, cleaned, and entered into Epi info version 7.2 statistical package, checked for completeness and exported to SPSS version 27 software for analysis. Kaplan–Meier survival analysis was used to estimate the median survival time across different variables. A log-rank test was used to compare the observed differences in survival time among different groups. The Cox proportional hazards regression model was used to identify predictors of mortality. Results were presented using adjusted hazard ratios along their corresponding 95% confidence intervals. A significant relationship was declared at p-value of <0.05. The assumption of a Cox regression proportional hazard model was checked using Log-Log survival plot test.

Key Words: Oncology, breast cancer, survival time, predictors, Ethiopia

1. Introduction

1.1. Background

Cancer is a major public health problem and a leading cause of death worldwide, accounting for 19.3 million incidences and nearly 10 million deaths in 2020. It affects people both in developed and developing regions. Breast cancer is the most common cancer and the leading cause of cancer mortality among women worldwide with an estimated 2.3 million new cancer cases and 685,000 cancer deaths in 2020 (1). It is responsible for 11.7% of total cancer cases and 24.5% of the cancers in females (2). Among females it accounts for 1 in 4 cancer cases and 1 in 6 cancer deaths, ranking first for incidence in the vast majority of countries (159 of 185) and for mortality in 110 countries (1). The high death rate warrants an improvement on cancer management medical facilities.

Cancer is a disease of the cells, which are the body's basic building blocks. Cancer occurs when abnormal cells grow and spread in an uncontrolled way (3). Most cancers start in a particular organ and are named after the body part in which they originated; thus, breast cancer refers to cancers originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk (4, 5). There are 5 major stages of breast cancer; the higher the number, the more the cancer has spread. Stage 0 is ductal carcinoma in situ, which is noninvasive but progresses to invasive cancer if left untreated, stages I-III are classified as early invasive stages (I, IIa, IIb) and locally advanced stages (IIIa, IIIb, IIIc), which are non-metastatic and stage IV is metastatic breast cancer which is treatable, but not curable (6, 7).

Evidences show that the comparatively low incidence rate of breast cancer in Africa had been rising over the years (8, 9). The mortality statistics showed Africa currently has the highest age-standardized breast cancer mortality rate globally, with the highest burden being recorded within the Sub-Saharan Africa (10, 11). The GLOBOCON 2020-based analysis reports the annual estimated 1.1 million new cases and approximately 711,429 deaths due to cancer in Africa in 2020. This report indicated that breast cancer was the leading malignancy, with 186,598 new cases (16.9% of total cases), which led to 85,787 deaths (12% of cancer deaths) (12).

According to the World Health Organization (WHO), breast cancer is the most common cancer among women in Ethiopia, accounting for 16,133 (32%) of all cancers (13). It is also the leading cause of cancer death among women in Ethiopia. The estimated number of breast cancer deaths in Ethiopia in 2020 was 9,061 which is nearly 18% of all cancer deaths. This number is expected to increase to 12,000 by 2030 (14). This calls for attention and the need for evidence to take urgent actions to mitigate the issue.

Exposure to exogenous hormones such as oral contraceptives, hormone replacement therapy (15), and dietary fat intake (16, 17) increases the risk of breast cancer. Despite the perception of all these risk factors, about 70% of females who develop breast cancer do not have identifiable risk factors (18). Previous studies revealed that tumor characteristics, metastasis, advanced disease stage, lymph vascular space invasion, multiple metastases, sites, endocrine therapy are predictors of survival of breast cancer patients (19, 20). Additionally, young age, late-stage at diagnosis, positive lymph node status, tumor size 3 and 4, and hormone receptor-negative status were associated with poor outcome (21).

The WHO has a global target of a 25% reduction in deaths from cancer and other non-communicable diseases in people aged 30–69 years to be achieved by 2025 (referred to as 25x25) (22). Similarly, United nation had planned to reduce premature mortality from non-communicable diseases including cancer by one third by 2030 (23). In line with this, Ethiopia has developed a National Cancer Control Plan in 2016 with a strategy to lower the incidence by increasing early detection and expanding treatment capacity to regional referral centers around the country. Since then, access to chemotherapy and endocrine medications has improved. For instance, the Ethiopian government and stakeholders have begun to fully equip 6 new regional oncology centers. However, these centers currently offer only a limited selection of chemotherapy treatment. (24)

Despite implementation of several strategies and significant advances in treatment, the treatment outcome of cancer is poor in the African setting due to lack of early detection, diagnostic facilities and inadequate treatment. The five-year survival rate in metastatic breast cancer is less than 30%, even with adjuvant chemotherapy (25). According to a study published in 2020, the five-year survival rate for breast cancer patients in Ethiopia is 25.8% (26), which is very low as compared to 91% in the United States (27).

1.2. Statement of the Problem

In the past two decades, published epidemiological reports in different parts of the world show significant increase in breast cancer mortality rate (28). In 1990, it was estimated that 59% of breast cancer cases occurred in more developed countries like North America, Europe, Australia, New Zealand and Japan (29). The situation changed considerably over the next two decades; by 2008, the total number of new diagnoses were evenly divided between more developed and less developed countries (8, 30) and by 2012 it was estimated that the majority (53%) of cases of female breast cancer were occurring in less developed countries (1). Although infectious diseases are the greatest burden for Sub-Saharan African countries, cancer incidence is growing at an alarming rate (31). The WHO reported around 70% of deaths in developing countries were due to cancer. Additionally, the GLOBOCAN 2020 report shows breast cancer is responsible for 30% of all cancers and 12% of mortality among females in Africa (32).

The burden of disease and economic impact of breast cancer is intensifying in low-middle income countries (LMICs) (33). Mortality in low-income countries, such as Fiji, Jamaica, Samoa, Nigeria, Cameroon, was higher than that in high-income countries- 41.0 per 100,000 population in Fiji to the lowest of 6.4 per 100,000 population in South Korea (34). This shift in the global distribution of cases and deaths highlights that breast cancer is continuing to emerge as a major health issue for women in Asia, Africa and South America (26, 35). Scholars are warning unless immediate action is taken, breast cancer will compound SSA's disease burden, worsen poverty and gender inequality as well as reverse the current global gains against maternal mortality (10).

Breast cancer also induces a substantial public health and economic burden, leading to a loss of 14.8 million Disability Adjusted Life Years (DALYs). The incidence of breast cancer is significantly higher in developed countries; globally, its age-standardized incidence rate was 54.5 per 100,000 female population in countries with high or very high Human Development Index (HDI) as compared to 31.3 in nations with low to medium HDI (36). But, the age-standardized mortality rates in low HDI countries were 1.5-fold higher than very high HDI countries (34).

In common with other developing countries, breast cancer mortality rate in Ethiopia is considerably higher than that of the developed world. It is the most common type of cancer, accounting for more than one third of all cancer cases among women and one-fifth of all national

cancer cases in the general population (37). In a study done in Ethiopia, 51% of deaths were attributed to non-communicable diseases; malignant neoplasm was the fourth leading cause of death which accounted for 10% of all deaths (38). The Addis Ababa cancer registry reports also show that breast cancer accounts for 32% of all female cancer cases. The national crude death rate of breast cancer was 9.8 per 100 person-years (39).

In many countries with advanced medical care, the five-year survival rate of early-stage breast cancers is 80–90 percent, while it falls to 24 percent for advanced stage (40). Five-year relative survival estimates ranged from 12% in parts of Africa to almost 90% in the United States, Australia and Canada (8). Five-year survival was 89% in Hawaii, 63% in Mexico, 51.8% in Uganda and 24% in Nigeria (41-44). Overall survival probability in Ethiopian women was 54.24% after two years and declined to 25.8% after five years with a median follow-up 15 months (26). The overall 5-year metastatic free survival (MFS) is 46% and the overall 2-year survival of patients with BC is 53% in rural Ethiopia (45). In a cohort study conducted in Ethiopia among 1070 females with breast cancer of stage 1-3, the 5-year MFS was 72% for stages 1 and 2 and 33% for stage 3. Young age and advanced stage were associated with poor outcome (21).

Despite the continued efforts and significant improvements, many barriers to breast cancer treatment exist and breast cancer treatment outcome is poor (46) (47). The condition is worse in developing countries due to the scarcity of healthcare resources and disparity in treatment and healthcare facilities (48). Although breast cancer is the most common cancer in women and has high mortality rate, limited evidence is available and there is a dearth of information regarding breast cancer treatment outcome and its predictors among Ethiopian breast cancer patients. The increasing breast cancer burden and wide variation in cancer survival between regions calls for the need for urgent investments in improving awareness, population-based cancer registration, early detection programmes, and health care infrastructure.

Although several studies have been undertaken in developed and developing countries like Ethiopia, there aren't enough studies about the predictors of treatment outcome. Those that were previously done used either different study designs or are done on small sample sizes, thus having low statistical power or missed some important variables that affect the outcome like socioeconomic and other tumor characteristics or failed to take into account some competing cases

of outcome/death and had a confounding bias. This study, therefore, will determine the survival time and the factors that predict the treatment outcomes in breast cancer patients in the Ethiopian set up using a different study design on adequate sample size, addressing all the important characteristics and taking into account confounders.

Breast cancer survival rates have been steadily increasing in the developing countries thanks to research. Similarly, this research will contribute as one of many researches to improve survival rates of breast cancer patients by improving the understanding on the predictors of breast cancer treatment outcome. While screening methods exist, there's always room for improvement. Hence, this research will help to identify risk factors and predictors and potentially lead to preventive measures, better screening and more accurate detection for early diagnosis as well as initiation of improved and more effective treatment options with fewer side effects.

1.3. Significance of the study

Early detection and treatment of cancer have a significant impact on the survival and mortality of cancer patients. Assessment of survival status and predictors of breast cancer treatment outcome can help to identify the most effective treatments for different types and stages of cancer. However, reports on the effectiveness of treatment in developing countries are rare. Different socioeconomic and cultural settings, budgetary constraints and limitations of resources have all been demonstrated to affect treatment outcomes. Thus, the findings of this study will help to improve our understanding of the factors that contribute to breast cancer treatment outcome and to develop more personalized and effective treatment strategies for breast cancer patients.

There have been quite a few studies; however, there is variation in the area, set up, population composition, management modality and several other factors that could contribute to the results observed. It is imperative to seek for the possible differences or similarities. Thus, this study will dive deep into this area and the results will be used to justify the current practice and the following outcome.

The results of the present study will help policymakers and other concerned bodies to plan and campaign for the awareness creation strategy and implementation of breast cancer screening programs. It will help them plan for the improvement of programs aimed at prevention and early

detection in the country. It will also help researchers to conduct related studies with more interventional study designs. It will be vital for the Federal Ministry of Health (FMoH) to plan programs and formulate cancer control strategies, prioritize cancer control measures, and assess the effectiveness and cost-effectiveness of these programs.

2. Literature Review

2.1. Survival Status

Five-year age-standardized net survival was broadly similar in the US (84%) and Europe **(**81%) (49) and was a bit higher in Australia (89.5%) (50). A similar study done in Brazil showed that the five-year overall breast cancer survival was 87.3% (51). A study done in Portugal reported that the estimated 5-year overall survival was 80% (52); that done in Vietnam shows that the five year survival status of patients with breast cancer was 74% (53). Furthermore, a study conducted in Central Iran, showed that survival rates at five years were estimated at 87.0% (54). International differences remain very wide, with levels as low as 51.07% in Indonesia (55) and 49.45% in Malaysia (56). One study conducted in Korea revealed the 5-year overall survival, local-relapse-free survival, distant-metastasis-free survival and disease-free survival rates were 95.3%, 97.2%, 91.3% and 88.5%, respectively (57).

Concerning Sub-Saharan countries, the five year survival status was 53.4% in South Africa, 30% in Cameroon (58), 11.9% in Gambia, 51.8% in Uganda (59) and 24% in Nigeria (44). Correspondingly, a study done in Kitui Hospital, Kenya, the overall mortality rate was 37.1%, while the overall rate of the censured event was 62.9%. It showed a higher number of patients had partial remission (43.1%) and disease progression (42.2%). The mean cancer-specific survival time was 25 ± 23.6 months. Furthermore, the percentage of survival was decreased from 82.8% in the first year to the 62.9% in the fifth year of treatment (11). In contrast, a study conducted in Kenya revealed that the mortality rate among breast cancer patients was 3%. Twenty-four percent of breast cancer patients had disease progression in the last follow-up. The mean cancer-specific survival was 11.4 months (32).

In a retrospective study done in southern Ethiopia, a total of 302 breast cancer patients were observed for 4685.61 person-months or at-risk time. Over a total follow-up time of 5 years, 67

patients died. The overall survival of breast cancer patients at the end of 3 years was 63.1%. The overall two-year survival of patients with Stage III and Stage IV disease was 73.4% and 44.3%, respectively. In this study, nearly three-fourths of breast cancer women had two years of overall survival (60). A retrospective cohort study showed that the overall survival of breast cancer patients at the end of five years was 25.8% (61).

In another study conducted in Ethiopia, a total of 410 participants were followed for a total of 60 months. The overall mortality rate was 16.9 per 100 person-year. The median survival time was 38.3 months. The survival estimation showed that the overall survival probability after breast cancer diagnosis was 11.42% at 60 months of follow- up (61). Another study done in Ethiopia showed that at the end of 3 years treatment follow-up, 46.53% of patients were dead, whereas 19.14% of patients were with an unknown outcome and 34.32% were alive (47).

A retrospective study done on 300 breast cancer patients in Ethiopia found that the overall survival rate at five years was 58.3% (61). On the contrary, a study conducted in northwest Ethiopia among 482 breast cancer patients found that the overall survival rate at five years was 25.8% (26). Another retrospective study that assessed the treatment outcome of 303 breast cancer patients at Black Lion Specialized Hospital Adult Oncology Unit from 2009 to 2014 found that the overall survival rate at three years was 34.32% (9).

2.2. Predictors

2.2.1. Socio-demographic Factors

Married status and low educational level were prognostic factors for higher mortality of women with breast cancer in a study done in Vietnam (53). In Indonesia, age, stage of disease, educational status and tumor size and location were the factors associated with the outcome (55) whereas in Malaysia were ethnicity and age at diagnosis (56). In the study done in Iran, age was a significant predictor (42) as the one conducted in Kenyatta Hospital where breast cancer patients above 60 years had 2.8 times more risk of dying than those below 60 years of age (32).

In a study conducted in southern Ethiopia, predictors of worse survival included rural residence and time to travel to the hospital for more than 7 hours (60). Similarly, in northwest Ethiopia place of residence was a significant predictor of mortality among breast cancer patients (61).

2.2.2. Clinical and pathological factors

A study done in Brazil showed that factors like stage at diagnosis**,** tumor size and positive margins affected the 5-year breast cancer-specific survival (51). A similar study conducted in Portugal revealed that there is a significant association with tumor stage (52) and the one done in Vietnam showed that late-stage at diagnosis was a factor that affected the treatment outcome (53). In Indonesia, the factors associated with the outcome were the stage of disease, tumor size and location (55). In Korea, the factor that affected the overall survival rate among others was the number of involved axillary lymph nodes (57). A number of LNs involved, size and side of the tumor, stage of disease and level of cellular differentiation were the significant predictors of mortality in a study conducted in Iran (62).

In a study done in Kenya, the size of the tumor was a statistically significant predictor of mortality among breast cancer patients. Breast cancer patients diagnosed at the advanced stage of the disease had 3.82 times more hazards of dying than an early stage of the disease (11). In addition, another study conducted in Kenyatta Hospital showed that breast cancer patients who had distant metastasis, and advanced stage of disease had 3.1 and 2.1 times more risk of dying than their counterparts, respectively (32).

A study conducted among 302 breast cancer patients in southern Ethiopia showed that symptoms of greater than 6 months and advanced stage of cancer were independent predictors of poor survival (63). Another study done in central Ethiopia revealed that the odds of death was decreased by 89% among patients who were diagnosed at early stage of the disease (stage 1 and 2) than those patients who were diagnosed at late stage of the disease (stage 3 and 4) (26). One done in Northwest Ethiopia showed that women with stage IV at baseline had a shorter median survival time than those in early clinical stages (I, II) and stage III. Furthermore, patients with histological grade I showed significantly better survival compared to those with other histologic grades. Additionally, patients with an increase in the number of positive lymph nodes involved had a higher risk of death (61).

2.2.3. Co-morbidities

Most observational studies have found that cancer patients with co-morbidities have poorer survival than patients without co-morbidities. Cohort studies with 5–7 years of follow-up have reported 1.1- to 5.8-fold higher mortality for breast cancer patients with any co-morbidity compared to patients with no co-morbidity (64). A study done in Kenyatta Hospital showed that breast cancer patients who had co-morbidity had 2.2 times more risk of dying than their counterparts (11).

Another study done in South Africa showed that advanced age with the co-morbidities and frail health as well as lack of support in the event of severe toxicity and the lack of availability of advanced pharmaceuticals and regimens, limited treatment options. Also, advanced stage at presentation and suboptimal induction therapy limited response rates (65). In a research conducted in northwest Ethiopia, patients with co-morbidities had a shorter median survival time than without co-morbidities (61).

2.2.4. Immunological Factors

Compared with HIV-negative women, women living with Human Immunodeficiency Virus (HIV), women living with HIV (WLWH), are diagnosed with breast cancer at a more advanced stage and have a worse overall survival in the elderly population according to a research conducted in the United States (66). And in a study conducted among 219 patients in Kenya, it was surprising to observe that HIV positive individuals were almost 3% less likely to develop metastasis after treatment compared to participants who were HIV negative (67).

2.2.5. Hormonal Factors

A study conducted in Portugal revealed that there is a significant association with presence or absence of hormone receptor and human epidermal growth factor receptor 2 (HER2) status (52). In another study done in Korea, the factors affecting the overall survival rate were the T stage, nuclear grade and c-erb B2 overexpression (57). A study done in Brazil showed that negative progesterone receptor affected the 5-year survival (51).

A study done in Kenyatta Hospital revealed that the presence of estrogen, human epidermal growth factor receptors and obesity were the independent factors influencing the development of

metastasis after treatment (32). A similar study done in Kenya showed that participants who had estrogen receptors, progesterone receptors and human epidermal growth factors were less likely to develop metastasis after treatment compared to those who did not have these receptors (67).

2.2.6. Therapeutic Factors

A study done in Brazil showed that factors like any other treatment but surgery combined with radiotherapy affected survival (51). One done in Vietnam showed that hormonal therapy reduced risk of death by approximately 80% (53). In a study done in northwest Ethiopia, the hazard of death for patients who took surgical therapy has 31% less risk of death than their counterparts who did not take surgical therapy (26). A study done in Hawassa revealed that poor adherence to adjuvant chemotherapy was one of the predictors of mortality (63).

In another similar study done in Ethiopia, number of chemotherapy cycle was found to have an association with treatment outcome in that the odds of death among patients who took less than 6 chemotherapy cycle was increased by 7.36 times than those who took 6 or more chemotherapy cycles. Similarly, the odds of death was reduced by 91% among patients who were on endocrine therapy than those who were not on endocrine therapy (26). One conducted in northwest Ethiopia showed women who had taken hormonal therapy had longer median survival time (41).

2.2.7. Reproductive Factors

In a study conducted in Hawassa, the hazard of death for premenopausal patients was 1.33 times higher as compared to postmenopausal patients (60). Likewise, study done in northwest Ethiopia revealed that premenopausal women had better survival time than postmenopausal women; postmenopausal women were 2 times more likely to die compared to premenopausal women (61).

2.2.8. Diet & Nutritional Factors

In a study done on 219 patients in Kenya, participants who were obese (Body Mass Index, BMI, 25-30) were 24% more likely to develop metastasis after treatment compared to those with normal BMI (67). A systematic literature review and meta-analysis of 82 follow-up studies revealed that obesity is associated with poorer overall and breast cancer survival in pre- and post-menopausal breast cancer and being overweight is also related to a higher risk of mortality. In this review,

obese and overweight breast cancer patients were 1.35 and 1.11 times, respectively, more likely to die than their counterparts (68).

A study conducted on the effect of diet on cancer recurrence suggested that a lifestyle intervention reducing dietary fat intake with modest body weight loss may improve the relapse-free survival of postmenopausal breast cancer patients. After approximately 5 years of follow-up, women in the dietary intervention group had a 24% lower risk of relapse than those in the control group (69). And according to a study on diet, dietary patterns, special diets, and specific dietary factors related to breast cancer survival and recurrence, adherence to high-quality diets and a prudent/healthy dietary pattern seemed to be beneficial for breast cancer prognosis (RR 0.74) whereas a Western/unhealthy diet was associated with poorer overall mortality (RR 1.44) (70).

2.3. Conceptual Framework

The following figure shows the interaction of different independent variables with the dependent variable. According to the literature review, these independent variables directly affect breast cancer treatment outcome, or the dependent variable.

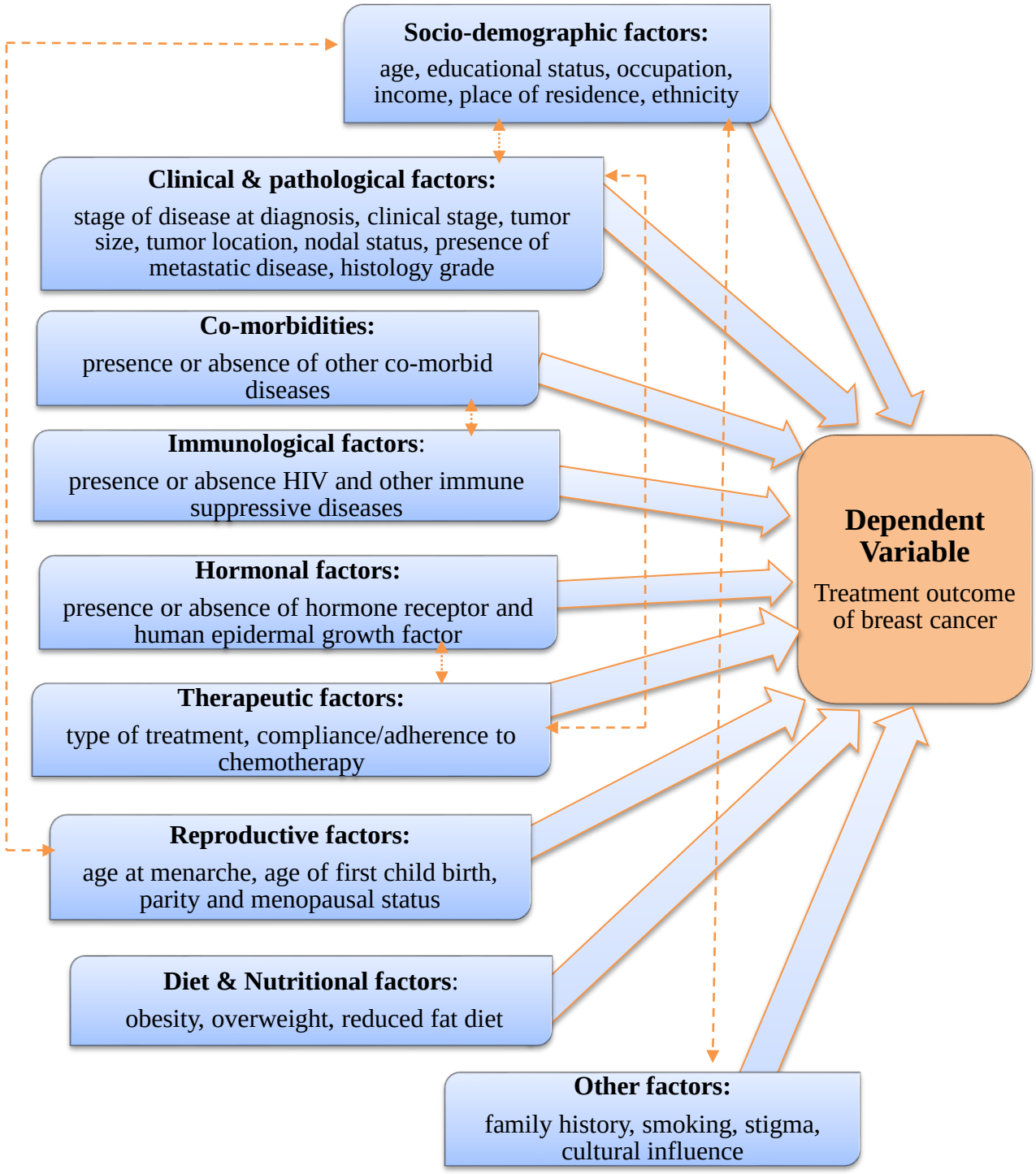

Figure 1. Conceptual Framework- this conceptual frame work is a diagrammatic representation of factors associated with breast cancer treatment outcome that is developed by the investigator based on different literatures (11, 26, 39, 47, 51-53, 60, 61, 64, 66, 67, 71, 72).

3. Objective of the Study

3.1. General objective

To assess the survival time and predictors of breast cancer treatment outcome at St. Paul's Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia, 2024.

3.2. Specific objectives

1. To estimate the median survival time of women with breast cancer at St. Paul's Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia, 2024.
2. To identify the predictors of survival time of breast cancer patients at St. Paul's Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia, 2024.

4. Methods

4.1. Study setting and period

St. Paul's Hospital Millennium Medical College in Addis Ababa is the first largest hospital in Ethiopia. The hospital provides a tertiary level referral treatment and is open 24 hours for emergency services. It is governed by a board under the Federal Ministry of Health. It has a catchment population of more than 1.5 million. The hospital has 2800 clinical, academic, administrative and support staff. It offers diagnosis and treatment for approximately 370,000-400,000 patients a year and has more than 700 beds with 130 specialists and 50 non-teaching doctors. The Adult Oncology Unit at St. Paul's Hospital Millennium Medical College provides comprehensive care for patients with cancer, including breast cancer. It has an outpatient department that renders service to new and follow-up patients as well as in-patients department with 350 beds. Breast cancer contributed to 19% of all malignancies admitted at St. Paul's Hospital Millennium Medical College from January to October 2023. The current study was conducted from January 2019 to December 2023.

4.2. Study design

A retrospective cohort study design was used.

4.3. Source Population

The source population were all patients diagnosed and enrolled in breast cancer treatment at the oncology unit of St. Paul's Hospital Millennium Medical College from January 2019 to December 2023.

4.4. Study Population

The study participants were all adult female patients diagnosed and enrolled in breast cancer treatment at the oncology unit of St. Paul's Hospital Millennium Medical College from January 2019 to December 2023 and who fulfill the eligibility criteria of the study.

4.5. Inclusion Criteria

All adult female breast cancer patients with a histologically confirmed diagnosis and who were treated in St. Paul's Hospital Millennium Medical College Oncology Unit from January 2019 to December 2023 were eligible to participate in the study.

4.6. Exclusion Criteria

Those who were male and who had incomplete medical records for the outcome and main exposure variables of the study were excluded.

4.7. Sample Size Determination

Sample size was determined using power analysis for sample size calculation for survival analysis using the formula:

$$\boldsymbol{d = \left(Z_{\alpha/2} + Z_{\beta}\right)^2 \frac{4}{In\Delta^2}}$$

$$\textbf{Total no of patients} = \frac{\boldsymbol{d}}{\boldsymbol{P(event)}}$$

Where:

- d= no of observed events
- Δ=Hazard ratio$= -\log\left(s(t)\right)$
- $s(t) =$ the survival probability $= 0.63$ (47)

- P (event): Probability of the event occurring within the study period
- α: Level of significance needed (chosen to be 0.05)
- β: Power of the study (90%)
- $Z_{\alpha/2}$: 1.96
- Z_{β}: 1.282

If we want to derive the total sample size required to yield 90% power to detect a hazard ratio of 0.463 ($\Delta = -\log(s(t)) = -\log(0.63) = 0.462$) based on a two-sided 0.05 level test, the required number of events were:

$$d = \left(Z_{\alpha/2} + Z_{\beta}\right)^2 \frac{4}{In\Delta^2} = (1.96 + 1.282)^2 \frac{4}{In(0.462)^2} = 71$$

Hence, $n = \frac{d}{P(event)} = \frac{71}{0.63} = 113$

Adjusting for a loss of 20%, $n_{adj} = \frac{n}{1-loss} = \frac{113}{1-0.2} \approx 142$

Thus, the total sample size required for the study was 142.

Previous studies were reviewed to calculate the sample size for the second analytic objective. A similar study conducted in northwest Ethiopia identified menopause status, presence of co-morbidity, stage at diagnosis, histology grade, number of LNs involved and hormonal therapy (41) to be predictors of breast cancer treatment outcome. Thus, a double population proportion formula is used to determine the sample size for the analytic objective considering each of the predictors. The formula for calculating n is:-

$$n_1 = n_2 = \frac{(Z_{\alpha/2}\sqrt{2\overline{pq}} + Z_{\beta}\sqrt{p_1q_1 + p_2q_2})^2}{\Delta^2}$$

The sample size is calculated using Epi info version 1.4.3 with the following assumptions:

- 95% confidence level
- power 80%
- Ratio of unexposed to exposed =1
- p_1= proportion of outcome among exposed

- p_2= proportion of outcome among unexposed
- q_1= 1- p_1
- q_2= 1- q_2
- α= level of significance needed
- β= power of the study
- $Z\alpha/2$= the corresponding Z-score for the selected confidence interval (level of significance)
- $Z\beta$= the corresponding Z-score for the selected power of study

After obtaining the sample size with the formula, 20% non-response rate was added.

Table 1**:** Sample Size with Double Population Proportion Formula for Analytic Objective and the Corresponding Sample Size with 20% Non-response Rate

Factors associated with treatment outcome	Confidence level	Power	Ratio of unexposed: exposed	Proportion of unexposed with outcome	AHR	Total sample size	Final sample size with 20% non-response rate
Stage at diagnosis- III	95%	80%	1	1.22%	9.43	216	260
Stage at diagnosis- IV	95%	80%	1	1.22%	10.44	188	226
Histology grade (grade III)	95%	80%	1	20.1%	2.12	150	180
No. of LNs involved	95%	80%	1	7.32%	4.78	82	99
No. of LNs involved- ≥10	95%	80%	1	7.32%	12.58	14	17
Hormonal therapy	95%	80%	1	15.54%	2.19	192	231

Finally, both were looked into to take the maximum sample size from the descriptive or analytic objective. The one with the maximum sample size was found to be the analytic objective, with stage at diagnosis (stage III) as a predictor.

- Thus, the final sample size is **260**, assuming a 95% confidence level, a proportion of 1.22% from previous study, a 5% margin of error and a 20% non-response rate.

4.8. Sampling Technique

All breast cancer patients who attended the oncology unit of St. Paul's Hospital Millennium Medical College from January 2019 to December 2023 were identified to serve as a sampling frame from which the participants were selected using simple random sampling method.

4.9. Data Collection Procedure

The data for this study was collected from the medical records of breast cancer patients at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia. A data extraction tool was prepared/developed based on the standard reporting parameters of cancer treatment outcomes and previous research findings. Then, the medical records of 307 eligible patients were retrospectively reviewed from the day of diagnosis to the end of the observation period. Trained nurses, extracted data from the patient's chart using the standardized data extraction tool. Data about socio-demographics, the time of breast cancer diagnosis, clinical characteristics, stage of disease, treatment details, outcome data and related factors were extracted.

Following the chart review, patients or their relatives were contacted through telephone. Out of 307 patients with BC, the phone number was not found for 27. Among 280 charts that have a telephone number, a telephone interview was made with 213 patients or with their close relatives who are ≥18 years of age. The rest of the phone call trials were not successful: there was a language barrier with 2 of them, 17 of them didn't respond for three or more call trials, 11 were unwilling to discuss, 14 were mistaken phone numbers, and the remaining 23 were not functional.

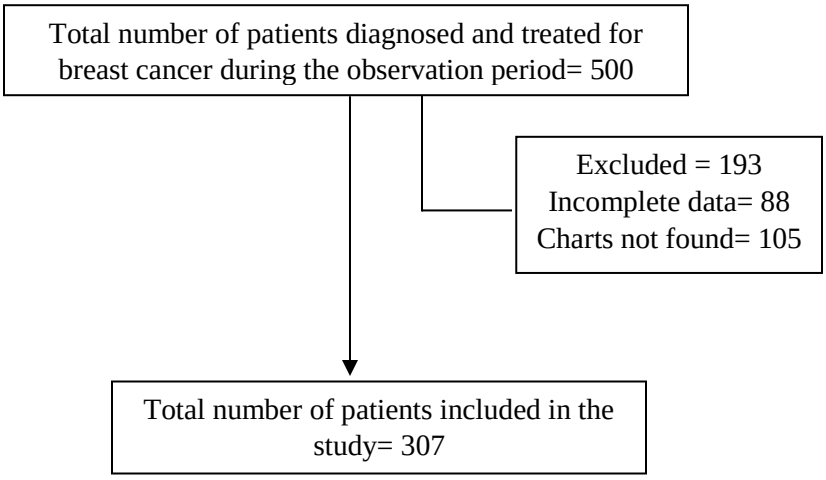

Figure 2. A flowchart illustrating the selection of study participants in the final analysis

4.10. Data Quality Assurance or Control

A pretest was done on 5% of the total sample size before conducting the actual data extraction to ensure the reliability and validity of the tool. The pre-test result helped to see the accuracy of the tool to obtain the required information from study participants. And the questionnaire was adjusted accordingly.

The principal investigator trained data collectors and supervisors for one day on the purpose of the study, methods of data extraction and keeping information confidential, and other basic principles related to data collection. The data collection instrument was prepared in English, and its consistency was checked.

The completeness of the questionnaire was checked by supervisors at the end of each day and double–checked by the researcher /principal investigator/.

4.11. Data Quality Management

Data quality assurance was maintained at three steps, before, during and after data collection period. First, before data collection period, one day training was given for the data collectors on the content of the data extraction tool, data collection method, ethical concerns and the purpose of the study. The principal investigator provided the training. The data extraction tool, prepared in English, was translated into Amharic and back to English to keep the consistency of the questions. Pretesting of the questionnaire was done to ensure the validity and reliability of data on 5% of the total sample size. Second, during data collection period, completeness and consistency of the data extraction tool was assessed daily by the field supervisors and the principal investigator. Supervisors and the principal investigator revisited the tool to check the accuracy of information collected by data collectors. Data entry and cleaning was performed as soon as data were collected which helped to identify the lacunae in the existing data, loss of follow-ups, and missing data points. Third, after data collection period, data was double-entered using Epi-Info software by two data clerks and inconsistencies, numerical errors and missing parameters of the entered data was reconciled by checking the questionnaire. Where discrepancies were observed, data entry was verified with the primary data source. Before any attempt for analysis was made, duplicates, missing values and outliers were checked by the principal investigator.

4.12. Data Analysis Procedure

Data was coded, cleaned, and entered into Epi info version 7.2 statistical package, checked for completeness and exported to SPSS version 27 software for analysis. The data was analysed as follows: Descriptive statistics was carried out to describe demographics, clinical and follow-up data. Data was summarized using frequencies and percentages for categorical covariates with a mean ± Standard Deviation (SD) or median with Inter Quartile Range (IQR) values for numerical variables as required after testing the assumption of normality using Kolmogorov-Smirnov test of normality where p-value of >0.05 indicated normal distribution. Time to death/censoring was calculated as mean survival time and Kaplan-Meier plots were used to compare survival experiences of different groups of patients by using survival and hazard curves. Log-rank test was used to identify the presence of significant difference in median survival time between different categorical independent variables. The association between the independent and outcome variables was analysed using Cox Proportional Hazard (Cox PH) regression model. Univarate Cox PH regression was run at a 25% level of significance to screen out potentially significant predictors/covariates. Multivariable Cox PH regression model was performed using the significant independent variables from the univariate Cox PH regression. To measure the presence and strength of association between the independent variables and the outcome variable/time to death/censoring, adjusted hazard ratio (AHR), p-value and its corresponding 95% CI were used. From the final model, variables with p-value ≤ 0.05 were considered to denote statistical significance.

The final multivariable Cox PH regression model was tested for proportional hazard assumption (model adequacy) using the Log-log function. It showed a good fit to the data, with a parallel survival curve for clinical stage throughout the period indicating proportionality of hazard.

4.13. Study Variables

4.13.1. Dependent Variable

- ✓ Time to death/censoring (in months)

4.13.2. Independent Variables

- ✓ Socio-demographic characteristics

- Age, educational status, occupation, income, place of residence, ethnicity, …

✓ Reproductive factors
- Age for marriage, age at first childbirth, menopause

✓ Clinical characteristics
- Stage of disease, duration of symptoms, tumor size, tumor location, nodal status, presence of metastasis, histologic grade, …

✓ Medical factors
- Treatment modality, number of chemotherapy cycle, type of chemotherapy, compliance/adherence, presence of co-morbidities

✓ Other factors
- Family history, smoking, stigma, cultural influence

4.14. Operational Definition

- **Survival status**: The outcome of patients at the end of follow-up time, dichotomized into censored or death that is sourced from the patient clinical data files from scheduled and unscheduled return visits.
- **Event**: The occurrence of death at any time during the follow-up period after the confirmed diagnosis of breast cancer.
- **Censored**: Breast cancer women, who were transferred out, lost follow-up, died from another cause, and did not develop the event at the end of the follow-up period.
- **Time to Event:** The time (in months) from the confirmed diagnosis of breast cancer to the date of death.

4.15. Ethical Issues

Ethical clearance was obtained from the Institutional Review Board (IRB) of Jimma University, College of Public Health and Medical Sciences. Before the start of data collection, ethical clearance was obtained from IRB of St. Paul's Hospital Millennium Medical College. The name and other personal identities of the patients were not recorded during the analysis to ensure the confidentiality of the data. Informed consent was not sought for this study. Since this was a secondary data and the data were to be collected retrospectively from the medical records of patients, consent was waived by the IRB itself.

5. Results

5.1. Socio-demographic Characteristics

Out of the 307 patients, more than half were primarily age 30-39 (26.7%) and 40-49 (30.3%). The majority of the patients were followers of the Orthodox religion (74.6%) and were married (82.7%). Addis Ababa was the residence of 169 patients (55.0%), followed by Oromia region (27.4%). Over half (53.4%) were unemployed, while 67 (21.8%) were housewives and 64 (20.8%) held formal employment in governmental or non-governmental organizations. (Table 2)

Table 2: Socio-demographic characteristics of breast cancer patients who were on treatment at the oncology unit of SPHMMC, Ethiopia, from January 2019 to December 2023 (n=307)

Variable		**Frequency**	**Percentage**
Age at diagnosis (in years)	<30	39	12.7
	30-39	82	26.7
	40-49	93	30.3
	50-59	47	15.3
	>=60	46	15.0
Religion	Orthodox	229	74.6
	Muslim	57	18.6
	Other	21	6.8
Marital status	Married	254	82.7
	Single	31	10.1
	Other	22	7.2
Place of residence	Addis Ababa	169	55.0
	Oromia	84	27.4

	Amhara	17	5.5
	Other	37	12.1
Occupation	Unemployed	164	53.4
	Employed	76	24.8
	Other	12	3.9

5.2. Comorbidity, Behavioral and Reproductive Characteristics

Of the 307 patients, 106 (34.5%) had one or more preexisting comorbidity. Hypertension was the most common comorbidity documented in 50 (16.3%) followed by diabetes mellitus in 22 (7.2%) and HIV in 12 (3.6%). More than one-third of the patients had abnormal body weight, with 26 (8.5%) being underweight, 66 (21.5%) being overweight, and 28 (9.1%) being obese. Only 22 (7.2%) admitted to using one or more substance. Of these, 22 were alcohol users, 4 were smokers, and 2 were khat chewers.

The mean age at menarche was 14.5 years (± 10.7). The majority (84.7%) had a history of pregnancy, with 175 (57.0%) being multigravida and 49 (16.0%) being grand multigravida. Furthermore, most were parous, with 38 (12.4%) being primipara, 181 (59.0%) being multipara, and 36 (11.7%) being grand multipara. The median age at first delivery was 20 years (IQR, 18-22). Nearly two-thirds (214, 69.7%) were premenopausal. Seventy-seven (25.1%) had a history of contraceptive use, either single or mixed methods, and 19 (6.2%) had a first-degree family history of breast cancer. (Table 3)

Table 3: Comorbidity, behavioral and reproductive characteristics of breast cancer patients who were on treatment at the oncology unit of SPHMMC, Ethiopia, from January 2019 to December 2023 (n=307)

Variable		**Frequency**	**Percentage**
Comorbidity	No	201	65.5

	Yes	106	34.5
	Hypertension	50	47.2
	Diabetes mellitus	22	20.8
	HIV	12	3.9
	Goiter	11	10.4
	Asthma	9	8.5
	Other cancer	8	7.5
	Others*	19	17.9
BMI (in Kg/m2)	<18.5	26	8.5
	18.5 - 24.9	187	60.9
	25.0-29.9	66	21.5
	≥ 30.0	28	9.1
History of substance use	No	248	80.8
	Unknown	37	12.1
	Yes	22	7.2
	Alcohol use	21	95.5
	Smoking	4	18.0
	Khat chewing	2	9.0
Age at Menarche (in years) (n=250) (Mean ± SD)	14.5 ± 1.07		
Gravidity	Nulligravida	47	15.3

	Primigravida	36	11.7
	Multigravida	175	57.0
	Grand multigravida	49	16.0
Parity	Nullipara	52	16.9
	Primipara	38	12.4
	Multipara	181	59.0
	Grand multipara	36	11.7
Age at first delivery (n=248) (Median, IQR)	20 (IQR, 18-22)		
Menopause status	Pre-menopause	214	69.7
	Post-menopause	93	30.3
History of contraceptives	No	133	43.3
	Unknown	97	31.6
	Yes	77	25.1
	OCP	20	26.0
	IUD	20	26.0
	Others	29	37.7
Family history of breast cancer	No	288	93.8
	Yes	19	6.2

N.B.: Others* include Dyslipidemia, Cardiac disease, liver, Pulmonary tuberculosis, renal disease, COPD, Stroke, Arthritis

5.3. Clinical and Pathological Characteristics

The primary breast complaint upon presentation was a breast lump, reported by 252 patients (82.1%). The median duration of the complaint was six months (IQR, 3-12). At diagnosis, the majority were classified as stage IIA (62, 20.2%), IIB (67, 21.8%), or IIIA (59, 19.2%).

Pathological examination revealed that 74 patients (24.1%) had a high nuclear grade (grade III), and invasive ductal carcinoma was the most common histologic type documented in 249 (81.1%). The majority presented with a unilateral tumor, with 145 (47.2%) on the right side and 153 (49.8%) on the left. Over half (53.1%) had a tumor ranging in size from 2 to 5 centimeters. Lymph node examination identified positive nodes in 203 patients (66.1%), with an average of 5 positive nodes (IQR, 2-8).

In addition, examination of estrogen, progesterone, and human epidermal growth factor (HER2) receptors revealed positive receptors in 116 (37.8%), 88 (28.7%), and 51 (16.6%) patients, respectively. (Table 4)

Table 4: Clinical and pathological characteristics of breast cancer patients who were on treatment at the oncology unit of SPHMMC, Ethiopia, from January 2019 to December 2023 (n=307)

Variable		Frequency	Percentage
Breast complaints at first visit	Breast lump	252	82.1
	Axillary swelling	18	5.9
	Others	37	12.1
Duration of complaint (in months) (Median, IQR)	6 (IQR, 3-12)		
Clinical stage TNM	0	18	5.9
	I	18	5.9
	IIA	62	20.2

	IIB	67	21.8
	IIIA	59	19.2
	IIIB	31	10.1
	IIIC	23	7.5
	IV	29	9.4
Nuclear grade (n=144)	I (Low grade)	11	3.6
	II (Intermediate grade)	59	19.2
	III (High grade)	74	24.1
Histology type	Invasive ductal carcinoma	249	81.1
	Invasive lobular carcinoma	11	3.6
	Ductal carcinoma in-situ	8	2.6
	Invasive medullar carcinoma	4	1.3
	Invasive papillary carcinoma	5	1.6
	Metaplastic carcinoma	3	1.0
	Other	27	8.8
Laterality of tumor	Left	153	49.8
	Right	145	47.2
	Bilateral	9	2.9
Tumor size (in cm)	<2	24	7.8
	2-5	163	53.1
	>5	120	39.1

Node status	Negative	104	33.9
	Positive	203	66.1
No of positive nodes (n=181) (Median, IQR)	5 (IQR, 2-8)		
Estrogen receptor	Negative	191	62.2
	Positive	116	37.8
Progesterone receptor	Negative	219	71.3
	Positive	88	28.7
HER2	Negative	256	83.4
	Positive	51	16.6

5.4. Treatment Related Characteristics

Surgical intervention was the primary management for 287 patients (93.5%), of which 56 (18.2%) underwent surgery alone, and the remaining 231 (75.2%) required additional treatments, including chemotherapy, radiotherapy, and/or endocrine therapy. The most common surgical procedures were modified radical mastectomy (MRM), which was performed in 110 (38.6%) patients, and MRM with Axillary Lymph Node Dissection (ALND), which was performed in 145 (50.9%) patients.

Chemotherapy was administered to 233 patients (75.8%), including adjuvant chemotherapy (ACT) in 198 (84.9%) and neo-adjuvant chemotherapy in 35 (15%). The average number of chemotherapy cycles was 8 (IQR, 6-8), and the median duration of chemotherapy was 6 months (IQR, 4-7). Twenty-nine patients (9.4%) required radiotherapy following surgery and/or chemotherapy and were referred to other hospitals for treatment due to the lack of radiation therapy services at the hospital.

Endocrine therapy was administered to 120 patients (39.1%), with tamoxifen being the most common therapy given to 90 patients (75.0%). The median duration of endocrine therapy was 24 months (IQR, 9.75-37.5). (Table 5)

Table 5: Treatment related characteristics of breast cancer patients who were on treatment at the oncology unit of SPHMMC, Ethiopia, from January 2019 to December 2023 (n=307)

Variable		Frequency	Percentage
Mode of treatment	Surgery alone	56	18.2
	Surgery + Other	231	75.2
	Non-Surgical	20	6.5
Type of surgery (n=285)	MRM	110	38.6
	MRM + ALND	145	50.9
	Others	30	10.5
Chemotherapy	No	74	24.1
	Yes	233	75.9
Type of chemotherapy (n=233)	ACT	203	87.1
	NACT	30	12.9
No of chemotherapy cycle	8 (IQR, 6-8)		
Duration of chemotherapy	6 (IQR, 4-7)		
Radiotherapy	No	278	90.6
	Yes	29	9.4
Endocrine therapy	No	187	60.9
	Yes	120	39.1

Type of endocrine therapy (n=120)	Tamoxifen	90	75.0
	Anastrozole	21	17.5
	Unknown	9	7.5
Duration of endocrine therapy	24 (IQR, 9.75-37.5)		

5.5. Censoring Status and Mean Survival Time

The patients were followed for a median of 22 months (IQR, 8-36). Of the 307 patients, 42 died, resulting in an event rate of 13.7%. The remaining 265 were censored, with 263 still alive at the end of the study and two lost to follow-up. The mean survival time was 68.7 months (95% CI = 64.7-72.9 months).

5.6. Comparison of Survival Experience

The survival experience of the patients was compared based on their baseline clinical characteristics to identify statistically significant differences in mean survival time.

The results showed that characteristics that are significantly associated with survival time were the clinical stage of the patients, estrogen receptor, and progesterone receptor. Accordingly, patients diagnosed at advanced stages (stage III or IV) had a significantly shorter survival time as compared to those diagnosed at earlier stages (Stage 0, I, or II) (**53.8 months vs. 74.2 months, p-value=0.005**). In addition, patients with positive estrogen and progesterone receptors were found to have a significantly shorter survival time as compared to those with negative results (**64.9 months vs. 65.8 months, p-value=0.019** for estrogen receptor and **65.3 months vs. 67.5 months, p-value=0.009** for progesterone receptor). (Table 6)

Table 6: Comparison of survival experience between groups among breast cancer patients who were on treatment at the oncology unit of SPHMMC, Ethiopia, from January 2019 to December 2023 (n=307)

Variable	**Survival outcome**		

		Death (n=42) N (%)	Censored (n=265) N (%)	Mean time to death (in months)	P-value
Menopause status	Pre-menopause	30 (71.4)	184 (69.4)	67.9	0.653
	Post-menopause	12 (28.6)	81 (30.6)	62.7	
Comorbidity	No	24 (57.1)	177 (66.8)	69.8	0.357
	Yes	18 (42.9)	88 (33.2)	58.3	
BMI (in Kg/m2)	<18.5	5 (11.9)	21 (7.9)	51.0	0.344
	18.5 - 24.9	21 (50.0)	166 (62.6)	71.4	
	25.0-29.9	11 (26.2)	55 (20.8)	61.7	
	≥ 30.0	5 (11.9)	23 (8.7)	59.4	
Gravidity	Nulligravida	3 (7.1)	44 (16.6)	65.2	0.306
	Primigravida	4 (9.5)	32 (12.1)	72.2	
	Multigravida	25 (59.5)	150 (56.6)	62.0	
	Grand multigravida	10 (23.8)	39 (14.7)	49.8	
Parity	Nullipara	3 (7.1)	49 (18.5)	65.8	0.509
	Primipara	6 (14.3)	32 (12.1)	69.6	
	Multipara	27 (64.3)	154 (58.1)	61.1	
	Grand multipara	6 (14.3)	30 (11.3)	51.4	
Family history of breast cancer	No	40 (95.2)	248 (93.6)	68.5	0.773
	Yes	2 (4.8)	17 (6.4)	63.7	
Clinical stage TNM	0 - II	16 (38.1)	149 (56.2)	74.2	**0.005***
	III - IV	26 (61.9)	116 (43.8)	53.8	
Estrogen receptor	Negative	30 (71.4)	161 (60.8)	64.9	**0.019***
	Positive	12 (28.6)	104 (39.2)	65.8	
Progesterone receptor	Negative	35 (83.3)	184 (69.4)	65.3	**0.009***
	Positive	7 (16.7)	81 (30.6)	67.5	

HER2	Negative	37 (88.1)	219 (82.6)	67.4	0.210
	Positive	5 (11.9)	46 (17.4)	64.5	
Mode of treatment	Surgery alone	5 (11.9)	51 (19.2)	61.3	0.141
	Surgery + Other	33 (78.6)	198 (74.7)	69.6	
	Non-Surgical	4 (9.5)	16 (6.0)	39.5	

Furthermore, the KM survival and hazard function graphs also showed that having advanced-stage breast cancer at diagnosis was associated with significantly shorter survival time throughout the observation period with the difference becoming huge with longer follow-up. (Fig 2)

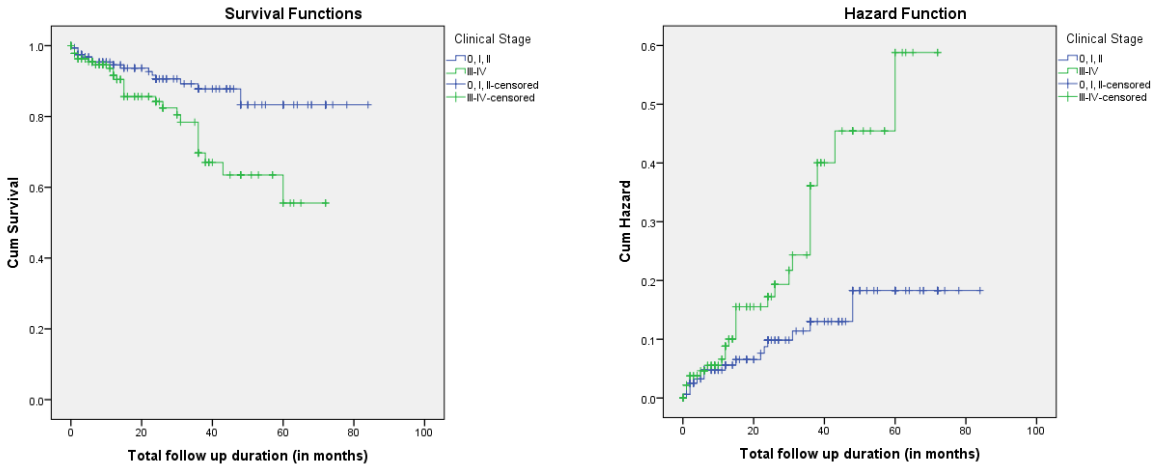

Figure 3: Kaplan-Meier survival and hazard curve of survival time stratified by clinical stage among breast cancer patients who were on treatment at the oncology unit of SPHMMC, Ethiopia, from January 2019 to December 2023

5.7. Predictors of Time to Death among Breast Cancer Patients

A Cox Proportional Hazards (PH) survival model was used to identify predictors of survival time among breast cancer patients. Initially, a univariate analysis was run at a 25% significance level and the following variables were found to be significant: menopause status, comorbidity, BMI, family history of breast cancer, clinical stage, estrogen receptor, progesterone receptor, HER2 receptor, and mode of treatment.

Subsequently, the final multivariable regression model was run at a 5% significance level, incorporating these significant variables. The results indicated that the clinical stage of the disease

at diagnosis was the only significant factor associated with survival time. Accordingly, after adjusting for other covariates, the rate of death among patients who presented with advanced disease (stage III or IV) was 2.40 times higher than patients who presented at earlier stages (stage 0, I, or II) (**AHR=2.40, 95% CI=1.25, 4.61, p-value=0.009**). (Table 7)

Table 7: Predictors of time to death among breast cancer patients who were on treatment at the oncology unit of SPHMMC, Ethiopia, from January 2019 to December 2023 (n=307)

Variable		**CHR (95% CI)**	**AHR (95% CI)**	**P-value**
Menopause status	Pre-menopause	1	1	
	Post-menopause	0.86 (0.44, 1.68)	0.65 (0.32, 1.34)	0.247
Comorbidity	No	1	1	
	Yes	1.33 (0.72, 2.45)	1.58 (0.81, 3.08)	0.184
BMI (in Kg/m2)	<18.5	1	1	0.339
	18.5 - 24.9	0.48 (0.18, 1.28)	0.52 (0.19, 1.41)	0.200
	25.0-29.9	0.80 (0.28, 2.31)	0.97 (0.33, 2.84)	0.948
	≥ 30.0	0.65 (0.19, 2.26)	0.61 (0.17, 2.19)	0.452
Family history of breast cancer	No	1	1	
	Yes	0.81 (0.19, 3.37)	0.70 (0.16, 2.99)	0.632
Clinical stage TNM	0 - II	1	1	
	III - IV	2.39 (1.28, 4.47)	**2.40 (1.25, 4.59)**	**0.009***
Estrogen receptor	Negative	1	1	
	Positive	0.46 (0.23, 0.89)	0.70 (0.29, 1.66)	0.422
Progesterone receptor	Negative	1	1	
	Positive	0.36 (0.16, 0.81)	0.42 (0.15, 1.19)	0.104
HER2 receptor	Negative	1	1	
	Positive	0.56 (0.22, 1.42)	0.77 (0.29, 2.03)	0.603
Mode of treatment	Surgery alone	1	1	0.517
	Surgery + Other	0.46 (0.12, 1.70)	0.97 (0.36, 2.60)	0.944
	Non-Surgical	0.37 (0.13, 1.04)	1.83 (0.46, 7.27)	0.389

N.B.: CHR= Crude Hazard Ratio, AHR= Adjusted Hazard Ratio, *= Statistically significant

To assess the proportional hazards assumption of the Cox regression model, a log-minus-log plot was generated using the significant variable from the final model. Parallel lines in this plot suggest that the assumption holds. As shown in Figure 3 below, the survival curves appear to be parallel across the observation period, indicating a reasonable fit to the proportional hazards assumption.

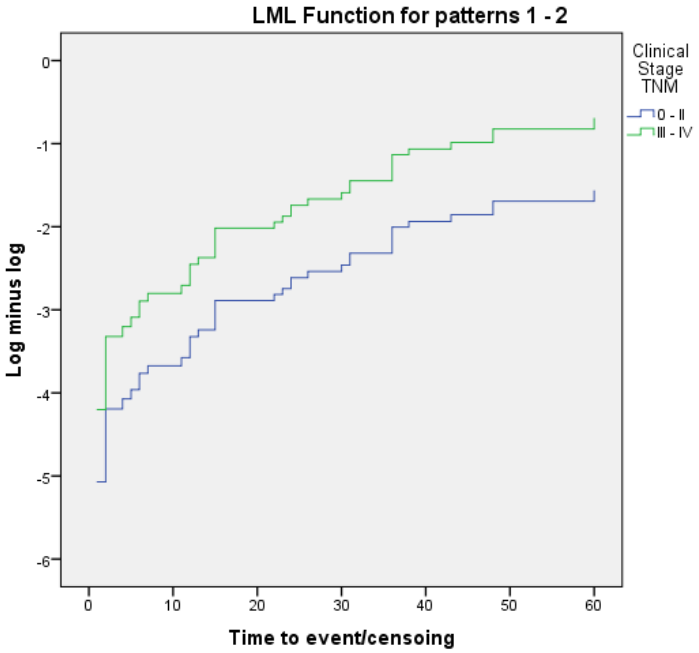

Figure 4: Log minus Log function of survival time stratified by clinical stage among breast cancer patients who were on treatment at the oncology unit of SPHMMC, Ethiopia, from January 2019 to December 2023

6. Discussion

The study aimed to assess the survival time and predictors of breast cancer patients who were on treatment at Oncology unit of one of the large tertiary referral hospitals in Ethiopia between January 2019 to December 2023. A total of 307 eligible patients were included in the study, of which nearly two-thirds (69.7%) were premenopausal and 106 (34.5%) had comorbidities. Most had a history of pregnancy (84.7%) and childbirth (83.1%), with a median age at first delivery of 20 years. Seventy-seven (25.1%) had used contraceptives, and 19 (6.2%) had a family history of breast cancer. At presentation, the primary complaint was a breast lump (82.1%), and the median

duration of complaint was six months. Most were diagnosed as stage IIA (20.2%), IIB (21.8%), or IIIA (19.2%), and invasive ductal carcinoma was the most common type (81.1%). Estrogen, progesterone, and HER2 receptors were positive in 116 (37.8%), 88 (28.7%), and 51 (16.6%), respectively. Surgical intervention was the primary management (93.5%), of which 18.2% underwent surgery alone and 75.2% required additional treatments. Chemotherapy was administered to 233 patients (85.9%), 29 (9.4%) required radiotherapy, and 120 (39.1%) received endocrine therapy.

The patients were followed for a median of 22 months (IQR, 8-36), during which time 42 patients died resulting in an event rate of 13.7%. This represents a lower mortality rate than reported in other African studies, where an overall mortality rate of 37.1% was observed in one study (11). Additionally, this study's mortality rate is lower than those reported by other Ethiopian studies, with rates as high as 46.5% for three-year follow-ups (9, 43) and over 70% for five-year follow-ups (22, 57). Furthermore, this study revealed a mean survival time of over five years (68.7 months, 95% CI = 64.7-72.9 months), indicating that a significant portion of the patients survived for a substantial period. This survival time is longer than reported in other studies conducted in Africa where a mean cancer-specific survival times of 25 months (11) and 11.4 months (28). While these studies included comparable study populations and sizes, the differences in mortality rate and survival time could be primarily attributed to the relatively longer follow-up duration in those studies compared to the current study. Subsequently, the difference compared to studies conducted in Ethiopia could also be attributed to the fact that this study was conducted at a tertiary-level hospital with a well-organized oncology clinic, well-trained specialists and subspecialists, and better follow-up services, all of which can contribute to improved patient outcomes.

The survival experience of the patients demonstrated that those diagnosed at advanced stages (III or IV) had less favorable outcomes than those diagnosed at earlier stages (0, I, or II), with a shorter survival time of 20.4 months. This finding was further confirmed by the multivariable Cox PH regression model, which identified clinical stage as the only significant predictor of survival time among breast cancer patients. The model revealed that patients presenting with advanced disease had a more than two-fold higher risk of death compared to those presenting at earlier stages. It is well-established that the clinical stage of breast cancer at diagnosis is a crucial prognostic factor, significantly influencing survival outcomes. Advanced disease at diagnosis is associated with a

higher risk of recurrence, poorer survival, and limited treatment options. In addition, advanced cancers tend to progress more rapidly and may be more resistant to treatment, further contributing to unfavorable outcomes. Studies conducted in various settings, including Ethiopia (26, 57, 59), other African countries (11, 28) and outside Africa (47, 48, 49, 51, 53, 58), have reported an increased risk of mortality for advanced-stage patients by up to three-fold.

6.1. Strengths and Limitations

Strengths of the study

This study contributes to the existing literature, as there are limited studies on survival outcomes of patients in this setting. Additionally, the study was conducted in of the country's largest oncology centers with a diverse patient flow and specialized services. Furthermore, the inclusion of a wide range of covariates enabled the control of multiple potential confounders.

Limitations of the study

The event rate was smaller, which could potentially impact the reliability of the estimates obtained.

7. Conclusion

The study revealed a relatively lower mortality rate and longer survival time. The only significant predictor of survival time among breast cancer patients was found to be the clinical stage of the disease at diagnosis. Advanced-stage patients experienced significantly shorter survival times and a higher risk of death.

8. Recommendations

Based on the findings of this study, the following recommendations are made**:**

Health Care Providers:

Encourage early detection and diagnosis of breast cancer through regular screenings and awareness campaigns. Promote the use of accurate staging systems to ensure timely and appropriate treatment decisions. Follow the implementation of national guidelines for breast cancer management to standardize care and improve outcomes.

Health Policy Makers:

Allocate adequate resources for breast cancer prevention, early detection, and treatment. Strengthen data collection and monitoring systems to track breast cancer incidence, mortality, and treatment outcomes.

Community Organizations:

Conduct public awareness campaigns to educate women about breast cancer risk factors, early detection, and the importance of seeking medical attention. Advocate for policies that support early detection, accessible treatment, and improved outcomes for breast cancer patients.

Researchers:

Conduct a longer-duration, multi-facility follow-up study to further investigate the factors influencing survival outcomes and identify potential areas for improvement. Conduct studies to identify reasons for delayed healthcare-seeking behavior and to improve early detection and treatment of breast cancer.

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10. Annexes

10.1. Information Sheet

Title of the Research: Survival Time and Predictors of Breast Cancer Treatment Outcome at St. Paul's Hospital Millennium Medical College, Oncology Unit, Addis Ababa, Ethiopia, 2024.

Name of Investigator: Ewnet Berhanu (BSc)

Name of the Organization: Jimma University

Introduction: My name is Ewnet Berhanu. I am conducting a study on breast cancer survival and treatment outcomes. I am going to give you information and invite you to be part of this research. You can participate if you are age 18 and above and are enrolled in breast cancer treatment at the oncology unit of St. Paul's Hospital Millennium Medical College from January 2019 to December 2023. If you agree to participate, you may be asked to complete questionnaires about your medical history, lifestyle habits, and demographics and allow researchers to access your existing medical records related to your breast cancer diagnosis and treatment. If you have any questions about this study, please do not hesitate to ask. I will be happy to take time and explain any terms you don't understand and answer your questions in detail.

Purpose: Breast cancer is the most common cancer among women. This research aims to investigate factors that influence how long women diagnosed with breast cancer survive and how well they respond to treatment. By collecting and analyzing various data points including demographic information, treatment regimens, and lifestyle factors, the study seeks to enhance our understanding of factors influencing survival rates and treatment efficacy. Ultimately, the findings may contribute to the development of more personalized and effective breast cancer treatment strategies.

Risks and/or discomfort: There are minimal risks associated with this study. Your participation will involve completing questionnaires about your medical history, lifestyle habits, and demographics. This may require some time and effort. Researchers may also access your existing medical records related to your breast cancer diagnosis and treatment. However, strict measures will be in place to ensure participant safety and confidentiality throughout the research process.

There may be a slight chance of encountering emotional discomfort while reflecting on your medical history. However, you are free to skip any questions that make you feel uncomfortable.

Benefits: There is no direct benefit to you from participating in this research. However, your contribution will be invaluable in helping us understand breast cancer survival and treatment outcomes. The findings from this study could lead to improved treatment strategies, better patient care for future breast cancer patients, and advancements in breast cancer research.

Confidentiality and Privacy: I take your privacy very seriously. All your information will be kept confidential. The confidentiality and privacy will be rigorously safeguarded throughout the study. Your name will not be linked to any data collected or published in research findings. All data collected will be anonymized, analyzed and stored securely in compliance with applicable laws and regulations. Only authorized research personnel will have access to participant information, and any published results will be presented in aggregate form to maintain anonymity.

Incentives/Payments for participating: You will not receive direct financial incentives for taking part in this study. However, you will have the opportunity to contribute to meaningful research aimed at improving breast cancer treatment outcomes, which can be inherently rewarding.

Right to Refuse or Withdraw: Participation in this study is entirely voluntary, and you have the right to refuse to participate or withdraw from the study at any time without penalty or without facing any negative consequences. You do not have to take part in this research if you do not wish to do so. You may change your mind later and stop participating even if you agreed earlier. And that will result in no harm. Your decision will be respected without question, and you will continue to receive standard medical care and treatment regardless of your participation status.

Who to Contact: This research will be reviewed and approved by the institutional review board/ committee of Jimma University and Addis Ababa Regional Health Bureau. If you have any questions you may ask now or later, even after the study has started. If you wish to ask questions, you may contact any of the following individuals (Investigator and Advisors) and you may ask at any time you want.

1. Ewnet Berhanu- Jimma University: Principal Investigator.
   E-mail: pomaberhanu@gmail.com

Cell phone: +251911744542

2. Yenealem Gezahegn- Jimma University: Advisor

   E-mail: juyene2@gmail.com

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3. Teshome Kabeta - Jimma University: Advisor

   E-mail: tka1204@gmail.com

   Cell phone: +251911436150

Your participation in this study is greatly appreciated and will contribute to advancements in breast cancer research. Thank you for considering being a part of this important endeavor.

10.2. Consent form

Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If Illiterate:

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____

Day/month/year

10.3. Questionnaire

Part 1: Socio- demographic variables

No.	Question	Option	Answer
1.	Age (years)		
2.	What is your educational status? ISCED classification.	1. Cannot read and write 2. Early childhood education 3. Primary school 4. Lower secondary education 5. Upper secondary education 6. Post-secondary non-tertiary education 7. Short-cycle tertiary education 8. Bachelors degree or equivalent tertiary education level 9. Masters degree or equivalent tertiary education level 10. Doctoral degree or equivalent tertiary education level	
3.	Weight		
4.	Height		
5.	Religion	1. Muslim 2. Orthodox 3. Catholic 4. Protestant 5. Other	
6.	What is your current marital status?	1. Married 2. Single/Not married 3. Separated	

		4. Divorced 5. Widowed	
7.	Residence	1. Addis Ababa 2. Outside of Addis Specify _____	
8.	Occupation	1. Private 2. NGO 3. Government employee 4. Unemployed 5. Student	
9.	Monthly income (in ETB)		

Part 2: Clinical and pathological characteristics

S. no	Question	Option	Answer
10.	Breast complain at first visit	1. Breast lump 2. Breast ulcer 3. Axillary swelling 4. Nipple retraction 5. Nipple discharge 6. Other	
11.	Duration of symptoms		
12.	Stage of cancer at diagnosis	1. I 2. II 3. III 4. IV 5. Unknown	
13.	Nuclear grade	1. I 2. II 3. III	
14.	Histology type	1. Invasive ductal 2. Invasive Lobular 3. Invasive Medullar	
15.	Deep surgical margin	1. Free 2. Involved	
16.	Laterality of tumor	1. Left 2. Right	

		3. Bilateral	
17.	Tumor size: _____ cm		
18.	Node status	1. Positive 2. Negative	
19.	Number of positive node _____		
20.	Estrogen receptor	1. Negative 2. Positive 3. Not stated	
21.	Progesterone receptor	1. Negative 2. Positive 3. Not stated	
22.	Human epidermal growth factor receptor	1. Negative 2. Positive 3. Not stated	
23.	Histological differentiation of tumor cell	1. Noninvasive Carcinoma a) DCIS b) LCIS 2. Invasive Carcinoma a) Ductal b) Lobular c) Medullar d) Tubular e) other	
24.	Clinical stage TNM – modified Stage at diagnosis (International Federation of Gynecology and Obstetrics System and the American Joint Committee)	1. 0 2. I 3. IIA 4. IIB 5. IIIA 6. IIIB 7. IIIC 8. IV	

Part 3: Co-morbidities

S. no	Question	Option	Answer
25.	Co-morbidities/Pre-existing medical diagnosis	1. Yes 2. No	

26.	HIV status	1. Positive 2. Negative 3. Unknown	
27.	Hypertension	1. Yes 2. No 3. Unknown	
28.	Diabetes mellitus	1. Yes 2. No 3. Unknown	
29.	Heart disease	1. Yes 2. No 3. Unknown	
30.	Renal disease	1. Yes 2. No 3. Unknown	
31.	Previous malignant cancer	1. Yes 2. No 3. Unknown	
32.	Hepatitis	1. Yes 2. No 3. Unknown	
33.	Asthma	1. Yes 2. No 3. Unknown	
34.	Anemia	1. Yes 2. No 3. Unknown	
35.	Lipid problems	1. Yes 2. No 3. Unknown	
36.	Liver disease	1. Yes 2. No 3. Unknown	
37.	Pulmonary TB	1. Yes 2. No 3. Unknown	
38.	Pneumonia	1. Yes 2. No 3. Unknown	
39.	COPD	1. Yes 2. No 3. Unknown	
40.	Stroke	1. Yes 2. No 3. Unknown	

41.	Arthritis	1. Yes 2. No 3. Unknown	
42.	goiter	1. Yes 2. No 3. Unknown	

Part 4: Treatment, follow-up and complications

S. no	Question	Option	Answer
43.	Mode of treatment given	1. Chemotherapy 2. Surgery with chemotherapy 3. Radiotherapy with Chemotherapy 4. Surgery with chemotherapy and Palliative 5. Other	
44.	If surgery was done, type of surgery		
45.	If surgery was done, date of surgery		
46.	If chemotherapy, a. what type		
	b. how many cycles		
47.	If chemotherapy, date of commencement of chemotherapy	_____/_____/_____	
48.	If chemotherapy, duration of chemotherapy		
49.	If chemotherapy, completion of treatment/adherence	1. Yes 2. No	
50.	Was radiotherapy given?	1. Yes 2. No	

51.	If radiotherapy, total dose of irradiation		
52.	If radiotherapy, date of commencement of radiotherapy		
53.	If radiotherapy, duration of radiotherapy		
54.	Was she on endocrine therapy?	1. Yes 2. No	
55.	If endocrine therapy, mention the drug		
56.	If endocrine therapy, date of commencement of treatment		
57.	If endocrine therapy, duration of treatment/total months of use		
58.	If endocrine therapy, completion of treatment/adherence	1. Yes 2. No	
59.	Radiation complications during radiotherapy	1. Hematological 2. Cutaneous 3. Neurological 4. Others, specify_____	
60.	Surgical complications	1. Lymphedoma 2. Neuropathy 3. Other	
61.	Recurrence of symptoms	1. Yes 2. No	
62.	If yes, after how long did symptoms reappear		
63.	If yes, was there second line treatment?	1. Yes 2. No 3. There was no recurrence	
64.	If yes:	1. Surgery 2. Radiotherapy 3. Chemotherapy	

		4. Radiotherapy & Chemotherapy 5. Surgery & Radiotherapy 6. There was no recurrence	
65.	If there was a second line treatment, write the details of the treatment regimens		
66.	Clinical, pathology or radiological examination of the breast (for recurrence)	1. Presence of the tumor 2. No tumor seen	
67.	How many total follow up visits during treatment?	1. Not at all 2. One 3. Two 4. Three 5. More than three	
68.	Initial visit date/Date of diagnosis		
69.	Last visit date		
70.	Total follow-up duration		
71.	Status of the patient?	1. Alive 2. Dead 3. Unknown	
72.	If dead, when?	1. During treatment 2. Just after treatment 3. Less than one year 4. 2-3 years	
73.	What was the cause of death?		

Part 5: Reproductive factors

No.	Question	Option	Answer
74.	Age at menarche (years)		
75.	Age at first delivery (years)		
76.	History of contraceptives	1. Yes 2. No 3. Unknown	
77.	If yes, which method?	1. Condoms 2. Oral pills 3. Injectable 4. IUD 5. Norplant 6. Tubal ligation 7. Others, specify ____	
78.	Gravidity		
79.	Parity		
80.	Menopause status	1. Premenopausal 2. Postmenopausal	

Part 6: Other factors

81.	Family history of breast cancer	1. Yes 2. No	
82.	Fear of stigma	1. Yes 2. No	
83.	Cultural influence	1. Yes 2. No	
84.	History of substance use	1. Yes 2. No	
85.	If yes to history to substance use,	1. Yes 2. No	
	History of smoking	1. Yes 2. No	
	History of alcohol use	1. Yes 2. No	
	History of khat chewing	1. Yes 2. No	

Assurance of Principal Investigator

The undersigned agrees to accept responsibility for the scientific ethical and technical conduct of the research project and for the provisions of required progress reports as per terms and conditions of the Faculty of Public Health in effect at the time of grant is forwarded as the result of this application.

Name of the student: __Ewnet Berhanu____

Date: _September 8, 2024_ Signature: _Electronically signed_

Approval of the first advisor: _____

Date: _____ Signature: _____

Approval of the second advisor: _____

Date: _____ Signature: _____