

**ADDIS ABEBA UNIVERSTY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF NURSING AND MIDWIFERY DEPARTMENT OF
NURSING, POSTGRADUATE PROGRAM**

**SURVIVAL STATUS AND PROGNOSTIC FACTORS
AMONG BREAST CANCER WOMEN AT SELECTED
HOSPITALS IN SOUTHERN ETHIOPIA, 2023**

BY BITSIET DESTA (BSC)

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APPROVAL SHEET

As a research advisor, I hereby certify that I have read and evaluated this thesis prepared under my guidance by Bitsiet Desta, entitled "**Survival status and prognostic factors among breast cancer women at selected hospitals in southern Ethiopia, 2023.**" I recommend that it be submitted as fulfilling the thesis requirement.

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ACRONYMS

AHR	-	Adjusted Hazard Ratio
BC	-	Breast Cancer
CHR	-	Crud Hazard Ratio
GBCI	-	Global Breast Cancer Initiative
HIV	-	Human Immunodeficiency Virus
LMIC	-	Low- And Middle-Income Countries
MSF	-	Metastasis-Free Survival
NLR	-	Neutrophil To Lymphocyte Ratio
NPI	-	Nottingham Prognostics Index
ODK	-	Open Data Kit
OS	-	Overall Survival

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ABSTRACT

Introduction: Breast cancer is the major cause of morbidity and mortality worldwide, particularly in countries with limited resources. Patients in developing countries, particularly Ethiopia, are less likely to survive due to delayed diagnosis and advanced-stage presentations. Several studies have been conducted on the prognostic factors among breast cancer patients in Ethiopia, but they cannot consider neutrophils to lymphocytes as the prognostic factor.

Objective: To assess the survival status and prognostic factors among Breast Cancer women at selected hospitals in southern Ethiopia, 2023.

Methods: A retrospective cohort study was conducted among 507 randomly selected breast cancer women in selected hospitals in southern Ethiopia. Two trained BSc nurses collected the data using an open data kit (ODK). Descriptive statistics were summarized using tables and graphs. The bivariable and multivariable Weibull regression models were used to identify the prognostic factors. The final model fitness was investigated using the Cox-Snell residual test, and the Schoenfeld residuals test was used to examine the proportional hazards assumption.

Results: The overall survival of breast cancer women at the end of two and three years was 54.5% and 23.9%, respectively. An excellent and good Nottingham prognostic score (AHR: 0.26, 95% CI: 0.12, 0.53) and (AHR: 0.39, 95% CI: 0.18, 0.81), chemotherapy (AHR: 0.59, 95% CI: 0.36, 40.93), metastasis (AHR: 1.89, 95% CI: 1.31, 2.74), advanced stages (AHR: 1.73, 95% CI: 1.19, 2.51), hormone therapy (AHR: 0.64, 95% CI: 0.44, 0.92), and lower neutrophil to lymphocyte ratio (AHR: 0.68; 95% CI: 0.47; 0.97) were the prognostic factors of breast cancer women.

Conclusion: This study revealed that the breast cancer survivorship rate was lower than that of an earlier study from Ethiopia. An increased ratio of neutrophils to lymphocytes at the time of diagnosis and a poor NPI were linked to a worse chance of survival for breast cancer women; this indicated that promoting early diagnosis of breast cancer and treatment could be important to improve the survival of breast cancer patients.

Keywords: breast cancer, survival, prognostic factors

CHAPTER I

1.INTRODUCTION

1.1 Background

Breast cancer arises in the lining cells (epithelium) of the ducts (85%) or lobules (15%) in the glandular tissue of the breast(1). In 2020, 2.3 million women were diagnosed with breast cancer, and 685 000 women died from its worldwide(2, 3).In Africa, there were 8% of all breast cancer diagnoses, but the mortality rate was far higher (4).The sociodemographic index's levels of population are closely related to the patterns and trends of incidence and mortality of breast cancer around the world. Urbanization and nutritional change in developing nations, which may have been changing lifestyle factors, showed increasing incidence rates of breast cancer (5).

Effective breast cancer treatment is available, with survival rates of 90% or greater, especially when the tumor is detected early(1).The World Health Organization's Global Breast Cancer Initiative (GBCI) thereby advocates health promotion, early detection, prompt diagnosis, and thorough breast cancer management (6).The initiative aimed to avert 2.5 million cancer deaths globally and reduce the annual worldwide breast cancer mortality rate by 2.5%. Despite this, underdeveloped countries have difficulty treating breast cancer because of a lack of diagnostic and therapeutic resources, which has led to a high mortality rate (6).

Breast cancer risk factors that can be modified include long-term use of oral contraceptives, obesity, excessive alcohol consumption, smoking, postmenopausal hormone therapy, and consumption of a diet high in animal fat. Risk factors that can't be modified include gender, age, the age at which menstruation began, family history, and genetic mutations(1).

Unfortunately, even if all of the modifiable risk factors could be reduced, the probability of developing breast cancer would only be decreased by a maximum of 30%(1).Thus, strengthening the healthcare system and encouraging the gradual adoption of universal health coverage, especially for low- and middle-income nations where cancer and non-communicable disease programs are frequently inaccessible and under-resourced, are important (7).

1.2 Statement of the Problem

Breast cancer is the fifth leading cause of cancer mortality worldwide; disproportionately, the burden is high in developing countries due to insufficient access to radiotherapy, surgery, and nursing care (2, 8). The incidence of breast cancer was twice as high in high-income countries as it was in middle-income and low-income countries (4). Nevertheless, the prognosis of breast cancer patients in low- and middle-income (LMIC) countries were poor; the survival rate for breast cancer for at least five years after diagnosis ranges from more than 90% in high-income countries to 66% in India and 40% in Africa (1).

In sub-Saharan Africa, breast cancer ranked second in terms of the cancer-related deaths of women (9). The survival rate of breast cancer patients ranges from 58% to 74% in Sudan (10) and Malawi (11), respectively. Similarly, studies from Ethiopia reported that the overall survival rate for at least 5 years after diagnosis ranges from 25.8% (12) to 72.1% (13). Studies reported that several factors such as sociodemographic factors (age, residence, educational status (13, 14)), tumor-related prognostic factors include (tumor size, lymph nodes, histologic grade, stage, having comorbidity (11, 15), estrogen and progesterone receptors and HER2/neu (erB-2) oncogene alteration (16, 17)) and clinical and treatment-related (neutrophil to lymphocyte ratio (18), chemotherapy and surgical therapy (12, 19)) were significantly associated the survival of breast cancer patients.

The Nottingham Prognostics Index (NPI) is a prognostic index that forecasts survival from treatable primary breast cancer. Based on the tumor's size, the number of nearby lymph nodes, and its grade, the NPI value is determined. For instance, the patient had stage A lymph node disease, grade I, and a 2 cm tumor size upon presentation. According to the NPI, the patient had an anticipated 5-year survival rate of 91% (20, 21).

In Ethiopia, the survival rate of cancer patients was low as compared to other low- and middle-income countries (13). To decrease women's premature deaths, significant improvements in the early identification and treatment of breast cancer are necessary.

The government of Ethiopia has made an effort to enhance the quality of life for cancer patients by increasing the number of treatment facilities. Despite the efforts, there are various challenges, including radiation therapy's inefficiency and scarcity, a lack of

qualified manpower, patients' delayed presentations, and the community's low level of knowledge (22).

Previous studies attempted to determine Ethiopian cancer patients' prognostic factors(12, 13). The Neutrophil-Lymphocyte Ratio (NLR) had not been considered by any of them as a prognostic factor. But studies found that the Neutrophil-Lymphocyte Ratio (NLR) was a significant predictor of overall survival(18).Therefore, this study aims to assess the survival status and prognostic factors among breast cancer women at selected hospitals in southern Ethiopia, in 2023

1.3 Significance of the Study

This study will add new insight into the prognostic factors for breast cancer patients and estimate the survival rate. The findings of this study could benefit patients by mitigating case management-related deaths if care providers' attention is given to those patients at high risk of death. The findings of this study will give important information to policymakers, program managers, and health professionals about the importance of health promotion and early detection. Moreover, the findings of this study will provide information for future research on the Nottingham Prognostic Index.

CHAPTER II

2. LITERATURE REVIEW

2.1 Overview of cancer

Global noncommunicable diseases mortality rate preceding the mortality rate of communicable diseases. Cancer is one of the non-communicable diseases which is the leading cause of morbidity and mortality(23, 24).Globally, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020,this figure is expected to be 28.4 million cases in 2040(2). Also, breast cancer is estimated to have over 3 million new cases and 1 million deaths every year because of population growth and aging alone by 2040 (4).

2.2 Survival rate of breast cancer women

Disparities in the survival of breast cancer have been identified, especially among countries with different levels of development(5). In high-income countries over 90% of breast cancer were survived for five years after the diagnosis, yet in low and middle-income countries this figure was low(25).A study conducted in Brazil among 2,273 patients showed that overall survival of 72.1% in five years and 57.8% in ten years(26).The overall survival rate was 97% and 89% at 2 years and 5 years, respectively, in a study conducted in the United Arab Emirates among 988 patients who were diagnosed and histologically demonstrated to have breast cancer(27).

A study conducted in India among 2192 patients with breast cancer reported5- and 10-year overall survival of 87% and 77% and disease-free survival rates of 76% and 68%, respectively(15). Likely, a study from Iran reported that the overall survival rate decreased over time and was estimated to be 0.98%, 0.94% 0.87%, and 0.76% at 2, 3, 5, and 10 years respectively following diagnosis for breast cancer(17).The disease-free survival percentage for patients was 86.1%, according to another study from Iran. Patients who received hormone therapy had disease-free survival rates in the 10th percentile that were 23.85 months higher than those of individuals who did not(16).

A study conducted in Malaysia among 549 cases of breast cancer showed that approximately half 257 (46.8%) of patients died. The median survival times for those presenting at stages III and IV were 50.8 and 6.9 months, respectively(19).

A study conducted in Sudan among 225 breast cancer women reported that the cumulative survival rate was 58% with a median follow-up period was 59.8 months. The 5-year OS rates for stages I, II, III, and IV were 71.5%, 82.4%, 56.5%, and 8.4%, respectively(10)

A study conducted among 1,070 patients at Addis Ababa (AA) University Radiotherapy Centre, in Ethiopia from 2005 to 2010 showed a distant metastasis-free survival (MFS) after 2 years of 74% with a median follow-up of 23 months(28). A retrospective cohort study of 482 women in northwest Ethiopia who had breast cancer was conducted from September 2015 to August 2020. At two and five years, patients with breast cancer had an overall survival rate of 54.24% and 25.8%, respectively (12). A prospective study involving 107 BC patients with histological confirmation who had surgery between 2010 and 2016 in rural western Ethiopia found that the probabilities of survival at 1 and 2 years were, respectively, 78 and 53%(29).

2.3 Prognostic factors

2.3.1 Sociodemographic

A study from the United States reported that age at diagnosis was an important factor for prognostication and treatment decisions in patients with breast cancer(3). Similarly, a study done in Ethiopia shows that young age at diagnosis was related to a worse clinical outcome compared to their older counterparts (29). On the contrary, a study done in China shows young age was an independent prognosis factor for the overall survival breast cancer of patients(14). The risk of death was also found to be 2.04 times greater in patients with breast cancer 65 years and older than it was in women under the age of 40 in a study conducted in Northwest Ethiopia(12).

According to a retrospective cohort study from Northwest Ethiopia, premenopausal women had a 1.33 times higher mortality risk than postmenopausal women(12). In addition, a study from the Tigray region showed that the residence of the patient is a strong predictor of the death of a breast cancer patient(13).

2.3.2 Pathological and tumor-related factors

A study from Turkey reported that the stage of disease at diagnosis was the strongest prognostic factor of disease-free survival of breast cancer women(30). Another study done in Malaysia revealed those with stage III and stage IV diagnoses had a 2.3- and 6.2-fold higher probability of mortality than those with stage I(19). Also, a study from the United Arab Emirates showed that the hazard ratio was 4.85 for patients with stage 3 compared to those with stage I(27).Likely, the histology of the tumor was one of the important markers of the patient's prognosis. A study done in Ethiopia shows patients with ductal carcinoma had the best MFS compared with the other entities (28).

The size of the tumor was also found to be an independent predictor of poorer survival and recurrence outcomes(31). Women who had large tumour sizes when they were first identified had a 2.76 times higher mortality risk than women without large tumour sizes, according to a study conducted in the United States of America(3). According to a retrospective study conducted in the United Arab Emirates, those with tumors grade III had a 10.24 % higher probability of dying than those with Grade I tumors(27).Similarly, a study from Ethiopia found that women with stage IV breast cancer had a 1.82-times higher probability of dying than those with stage I breast cancer(12).

Several studies reported that lymph node involvement has been associated with a lower survival rate(15, 26, 32). A study from Brazil shows the risk of death was 2.35 times higher among lymph node-positive patients as compared to their counterparts(31).A study from Brazil showed that the presence of metastases has been associated with a lower survival rate(31). A meta-analysis and systematic analysis from China reported that women who had been diagnosed without metastasis cancer were a reduced risk of death by 45%(18).

Even although, estrogen receptor positivity demonstrates better prognosis in patients who received endocrine therapy(11). A study done in Ethiopia shows the mortality risk was 32% higher among estrogen receptor-negative patients as compared to estrogen receptor-positive breast cancer patients(33). Similarly, studies reported that survival was worse in patients with triple-negative breast cancer compared to non-triple-negative breast cancer(11, 34).

2.3.3 Treatment and Clinical-related Factors

Evidence indicated that radiotherapy and hormone therapy were associated with an increase in the survival rate(3). A study from Brazil reported that adjuvant radiotherapy has reduced the risk of death by 30%(31). Another study from Brazil revealed that, compared to other therapies (77%, 57.1%, and 37.5%), surgery alongside radiotherapy considerably improved 1-, 2-, and 5-year survival (99%, 94%, and 90.6%, respectively). Surgery alone raised the probability of death by seven times when compared to treatment with radiation (35). Adjuvant chemotherapy was beneficial to OS for grade II/III and T1c BC(36). According to a French study, adjuvant treatment decreased both the relative risk of distant metastasis and death by 25% and 18%, respectively(37). Also, a study from China showed that chemotherapy was associated with a 36% and 21% risk reduction on OS and BCSS, respectively(38).

In addition, a study from the USA showed that women who had received hormone therapy reduced the risk of death by approximately 10%(3). Similarly, a study from Brazil showed that hormone therapy reduced the risk of death by 59%(31). According to a retrospective study from Gonder, patients who had surgical therapy had a 31% lower probability of death than their non-surgery therapy counterparts (12). On the other hand, a Malaysian study found that the mortality risks for patients who did not undergo surgical intervention were two times higher than those for patients who did(19).

The neutrophil-to-lymphocyte ratio was a strong prognostic factor for overall disease-free survival. According to a meta-analysis report patients with elevated NLR were associated with a high risk for overall survival(18). Moreover, having coexisting medical conditions reduced the probability of survival(39). A study from Malawi shows women who had HIV positive was 5.51 times higher hazards of death as compared to their counterparts(11).

2.4 Conceptual formwork

The diagram below is the conceptual framework of the study and developed by reviewing related literature(11, 15, 27, 40), to determine the survival status and prognostic factors of breast cancer women. The explanatory variables are demographic, pathological, clinical, and treatment-related factors associated with the survival of the patients. Their interaction was checked by the multicollinearity assumption.

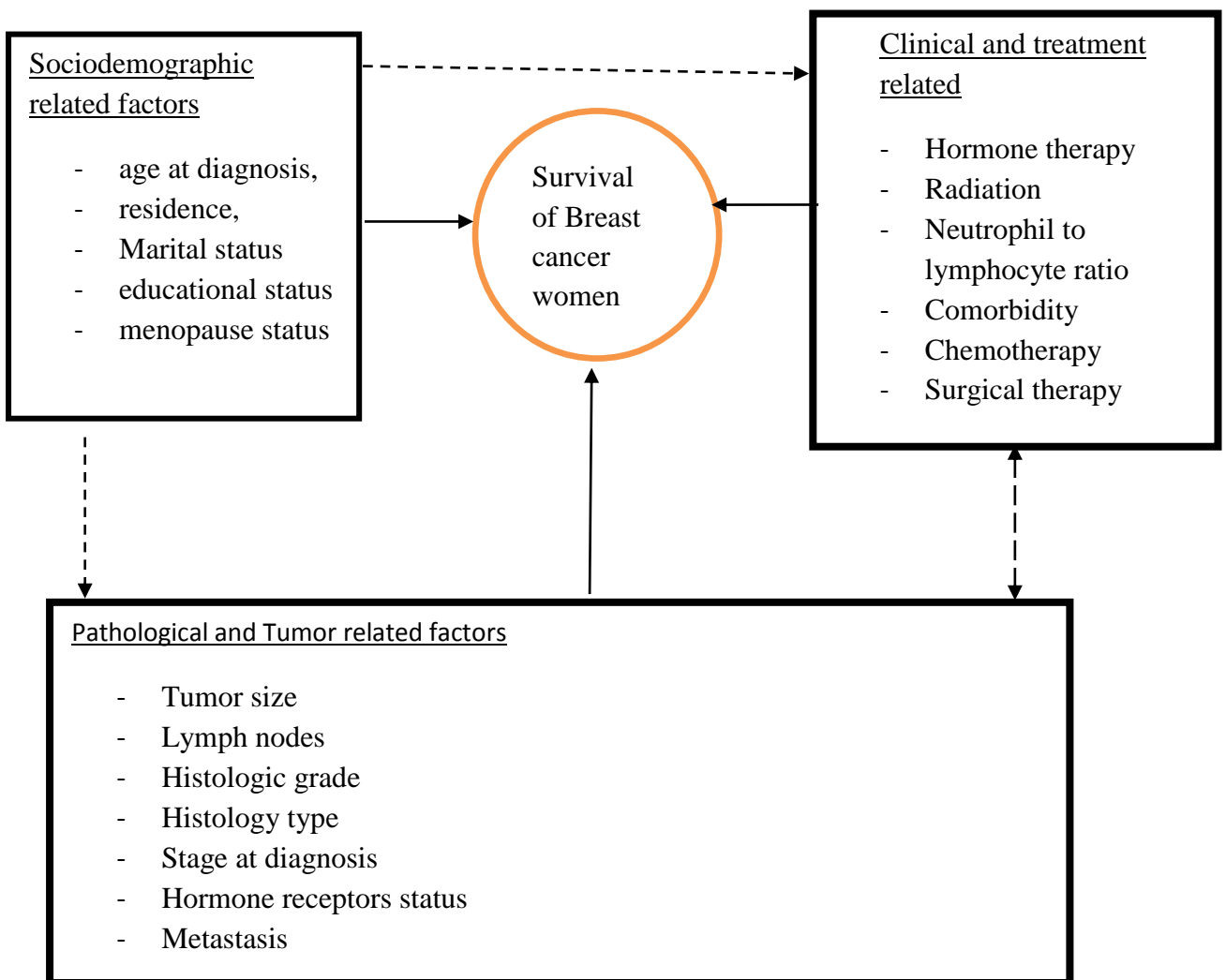


Figure 1 Conceptual framework of the study to assess survival status and prognostic factors of breast cancer women in southern Ethiopia, 2023

CHAPTER III

3. OBJECTIVES

3.1 General objective

- To assess Survival status and Prognostic Factors among BreastCancer Women at selected hospitals in SouthernEthiopia

3.2 Specific objectives

- To assess the Survivalstatus among Breast Cancer Women in Southern Ethiopia
- To identify Prognostic Factors Among Breast Cancer Women in Southern Ethiopia

CHAPTER IV

METHODS AND MATERIALS

4.1 Study area and period

This study was conducted at Hawassa University Comprehensive specialized hospital (HUCSH) and Wolaita Sodo University Comprehensive specialized hospital (WSUCSH). HUCSH is found in Hawassa City, 273 Km far south of Addis Ababa, Ethiopia. HUCSH, which has 650 beds, has been offering palliative and curative care to patients from the Sidama region and other neighboring areas. Twenty-five health professionals are working at the oncology unit (14 bachelor nurses, 2 general practitioners, 2 oncologists, 2 oncology nurses, 2 laboratory technicians, and 3 pharmacies).

WSUCSH, which is located 365 kilometres south of Addis Ababa and contains 420 beds for inpatient services, has been providing palliative and curative care. Thirteen health professionals are working in the oncology unit (8 bachelor nurses, 4 general practitioners, and one Oncologist). A total of 1950 women received breast cancer treatment in these hospitals. This study was conducted from March 1st to 30th 2023

4.2 Study design

A retrospective cohort study was conducted.

4.3 Population

4.3.1 Source population

All medical records of women diagnosed with breast cancer in Hawassa and Wolaita Sodo Comprehensive Specialized Hospitals.

4.3.2 Study population

All medical records of women diagnosed with breast cancer who attended the oncology department at Hawassa and Wolaita Sodo Comprehensive Specialized Hospitals, from 1st January 2020 to 31st December 2022.

4.4 Eligibility criteria

4.4.1 Inclusion criteria

All women with confirmed breast cancer admitted and treated at Hawassa University Comprehensive Specialized Hospitals and Wolaita Sodo University Comprehensive

Specialized Hospital with a complete medical record during the period were included in the study.

4.4.2 Exclusion criteria

Clients with incomplete records regard to baseline clinical characteristics (stage, tumor size, nodule status), unknown outcome status, and no telephone was excluded from the study. Also, clients whose medical charts are lost were excluded from the study.

4.5 sample size calculation and sampling procedure

4.5.1 Sample size determination

The minimum sample size required using an exponential model considering the following assumptions; type I error of 5%, power of 90%, and pre-menopausal status [AHR=1.33](12) was 461. After adding a 10% contingency for missing and incomplete data, the sample size for this study will be 507. The following STATA 16 command is for determining the sample size.

```
power exponential, hratio (1.33) effect(hratio) power (0.8) nratio (2)
```

5.1.2 Sampling procedure

The sampling frame was prepared after collecting the medical registration or identification number of patients from the registration books or electronic database of each hospital. Based on the number of women who received treatment, the sample size was proportionally allocated among the hospitals. By using proportionate allocation, 183 and 325 breast cancer women were selected from WSUCSH and HUCSH, respectively. Finally, the study participants were selected by a simple random sampling technique using computer-generated random numbers.

4.6 Study variables

Dependant variable (survival of breast cancer women)

Independent variables

- **Sociodemographic factors** included age at diagnosis, residence, education, family history, and menopause status
- **Tumor-related prognostic factors** include (tumor size, lymph nodes, histologic grade, stage, estrogen, and progesterone receptors, and HER2/neu (erB-2) oncogene alteration

- **Clinical and treatment-related** (Type of initial treatment, hormone therapy, radiation, neutrophil to lymphocyte; comorbidity, chemotherapy, and surgical therapy)

4.7 Operational definition

- **Event:** the occurrence of deaths from the first confirmed diagnosis of breast cancer to the end of the study.
- **Censored** –discharged with medical advice and lost to follow-up and alive at the end of the follow-up from first confirmed diagnosis of breast cancer
- The Nottingham Prognostics Index (NPI) value is calculated based on the size of the tumor, the number of lymph nodes, and the tumor grade (20, 21).
- $NPI = \text{maximum invasive cancer size (S)} \times 0.2 + \text{lymph node stage (LN = 1, 2, or 3)} + \text{histological grade (H = 1, 2, or 3)}$. Patients were grouped into four categories according to the NPI score: I (excellent) ≤ 2.4 ; II (good) > 2.4 but ≤ 3.4 ; III (moderate) > 3.4 but ≤ 5.4 ; and IV (poor) > 5.4 .
- **Stage at diagnosis:** The American Joint Committee on Cancer TNM classification scheme for staging breast cancers was used(41).
- **Prognostic factor-** is a characteristic of women that can be used to forecast the probability of recovery/ death from a disease(17)

4.8 Data Collection Instruments and Procedures

4.8.1 Data collection instrument

The English version data extraction checklist was designed from related literature (12-14, 28). The checklist consists of demographic factors included(age at diagnosis, residence, education, family history, and menopause status), tumor-related prognostic factors include (tumor size, lymph nodes, histologic grade, stage, estrogen, and progesterone receptors, and HER2/neu (erB-2) oncogene alteration, clinical and treatment-related (Type of initial treatment, hormone therapy, radiation, neutrophil to lymphocyte; comorbidity, chemotherapy, and surgical therapy and treatment outcomes consist of death, loss to follow up or alive.

4.8 Data Collection Procedures

Data were extracted from registers, patient cards, electronic databases, and operation notes using a data extraction tool for the occurrence of the event. Until December 31st, 2022, the endpoints for the follow-up were the dates of death, loss to follow-up, and the last

contact. The follow-up started on the day when the initial confirmed diagnosis of breast cancer was made. All charts of breast cancer patients, diagnosed between 1st January 2020 to 31st December 2022 at WSUCSH and HUCSH were reviewed from cancer registries. The record of all study participants will be selected according to the eligibility criteria. The outcome status of patients was obtained from the medical record and telephone interview. The median survival time was calculated as the time between the date of diagnosis of breast cancer to the date of death or the end of the 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. The data were collected by two trained BSc Nurses by using ODK collect.

4.9 Data quality assurance

A pre-test was done on 5% of the study sample patient chart at Tikur Anbesa Specialized Hospital to check for the existence of variables in the registration format on the patient's chart. Before the data collection period, one day of training was given to data collectors and supervisors. Onsite supervision was given to solve any doubts with data collection tools and techniques. The collected information was checked for consistency and completeness on the same day by the principal investigator. Reviewed cards were boldly marked to avoid re-review. Data cleaning was checked by the codebook for any missing values and data errors

4.10 Data Processing and Analysis

Data were collected by using ODK collect version 1.25.2 and then export to STATA version 16 for analysis. Descriptive statistics including proportions, median, tables, and charts were used to describe the characteristics of the study participants. The log-rank test and the Kaplan-Meier curve of survival were used to estimate the patients' probability of surviving.

Different models with different distributional assumptions were also compared to identify the best model, and finally, a model with the lowest AIC and BIC, which is the parametric survival test with Weibull distribution, was used to generate the estimates. A parametric survival analysis using Weibull regression was used to identify prognostic factors of BC patients. Crude and adjusted hazard ratios with their 95% confidence interval (CI) were estimated, and a p-value less than 0.05 was used to declare the presence of a significant

association. The proportionality assumption was tested by a global test based on Schoenfeld residuals.

4.11 Ethical consideration

The data from the data database and chart used in the study were routinely used for patient record data. The Addis Abeba University College of Health Sciences ethical review committee approved, and the Wolaita and Hawassa University Comprehensive Specialised Hospital granted consent. No patient agreement was sought because the study was carried out through a review of health records. The personal informant was kept anonymous throughout the investigation, and information concerning particular personal identifiers like patient names was not collected.

4.12 Dissemination plan

After the completion of the study, the results will be defended to Addis Ababa University, College of health science, School of Nursing and Midwifery, and the finding will be disseminated to concerned bodies of the studied hospitals, and other concerned stakeholders. An effort will be made to present this study in different symposiums and the paper will be sent for peer-reviewed publication.

CHAPTER V

5. RESULTS

5.1 Sociodemographic characteristics

A total of 492 breast cancer patients were included in this study, which yielded a 97% response rate. More than half, 54.27%, of the study's participants, were women between the ages of 35 and 50, with a median age of 40 and an interquartile range (IQR) of 34 to 49 years. The majority, 290 (58.94%) of the women were rural residents, and 138 (25.05%) of them had never attended school. More than two-thirds (73.37%) of women lived together, and more than a quarter (26.42%) of women were postmenopausal (**Table 1**).

Table 1: Sociodemographic characteristics of breast cancer women in southern Ethiopia, 2023

Variables	Category	Frequency	Percent
Age	<35 years	125	25.41
	35-50 years	267	54.27
	50+years	100	20.33
Residency	Urban	202	41.06
	Rural	290	58.94
Educational status	No formal education	138	28.05
	Primary school	164	33.33
	Secondary school	127	25.81
	Collage and above	63	12.80
Marital status	Single	47	9.55
	Married	354	71.95
	Divorced	50	10.16
	Widowed	41	8.33
Menopausal status	Premenopausal	362	73.58
	Postmenopausal	130	26.42

5.2 Clinical, histopathological, and treatment characteristics

At the time of diagnosis, 390 (79.27%) of the women had invasive ductal carcinoma (IDC), the most common histological type of breast cancer, and nearly two-thirds (63.82%) of the women had advanced stages of breast cancer. A third (33.54%) of women had a higher ratio of neutrophils to lymphocytes and nearly half (45.12%) of women had a

poor Nottingham prognosis index. Among the BC patients, 177 (35.98%) had undergone breast surgery, and of those, 120 (67.8%) had a modified radical mastectomy (MRM), 33 (18.64%) had a partial mastectomy, and 12 (6.77%) a "toilet" mastectomy. Of the 417 (84.76%) BC patients who had received chemotherapy, only 85 (20.38%) had finished it (good adherence). After the diagnosis of BC, 288 (58.54%) patients waited longer than a month before beginning chemotherapy, and 51.42% of them had distant metastasis cancer(**Table 2**).

Table 2:Clinical, histopathological, and treatment characteristics of Breast cancer women in southern Ethiopia, 2023

Variables	Category	Frequency	Percent
Stage of breast cancer at diagnosis	Early	178	36.18
	Advanced	314	63.82
Co-morbidities	Yes	90	18.29
	No	402	81.71
NLR	1-3	327	66.46
	>3	165	33.54
NPI	I	76	15.45
	II	53	10.77
	III	141	28.66
	IV	222	45.12
Histological type	Ductal	390	79.27
	Lobular	82	16.67
	Others	20	4.07
Distant metastasis	Yes	253	51.42
	No	239	48.58
Nodal status	Positive	241	48.98
	Negative	251	51.02
Surgical therapy	Yes	177	35.98
	No	315	64.02
Type of surgery(n=177)	MRM	120	67.8
	Toilet mastectomy	12	6.77
	Partial mastectomy	33	18.64
	Others	12	6.77
Deep surgical margin	Free	338	68.70
	Involved	154	31.30
Chemotherapy	Yes	417	84.76
	No	75	15.24
Adherence to chemotherapy(n=399)	Good	85	20.38
	Poor	332	79.62
Hormonal therapy	Yes	221	44.92
	No	271	55.08
Hormonal therapy type	Tamoxifen	167	75.57
	Anastrozole	54	24.43
Radiation therapy	Yes	22	4.47
	No	470	95.53
Waiting time to start	< 1 month	204	41.46

treatment after Dx	>1 month	288	58.54
NPI: Nottingham prognosis index: NLR: of neutrophils to lymphocytes			

5.3 Survival status of patients with breast cancer

A total of 492 BC patients were followed for a minimum of 1 month and a maximum of 38.2 months. During the follow-up period, 152 [30.8% (95% CI: 26.8; 34.9%)] died, 283 [57% (95% CI: 53.1%; 61.8%)] were alive, and 59 [11.5% (95% CI: 8.7–14.4)] were lost from the follow-up. The total time at risk for 492 was 5,634.9 person-months. The median survival time was 28.1 months, with an overall incidence rate of 2.6 (95% CI: 2.3, 3.1) per 100-person-month observation. The overall survival at the end of 1 year was 71.8%, at 2 years 54.5%, and at 3 years it was 23.9% (

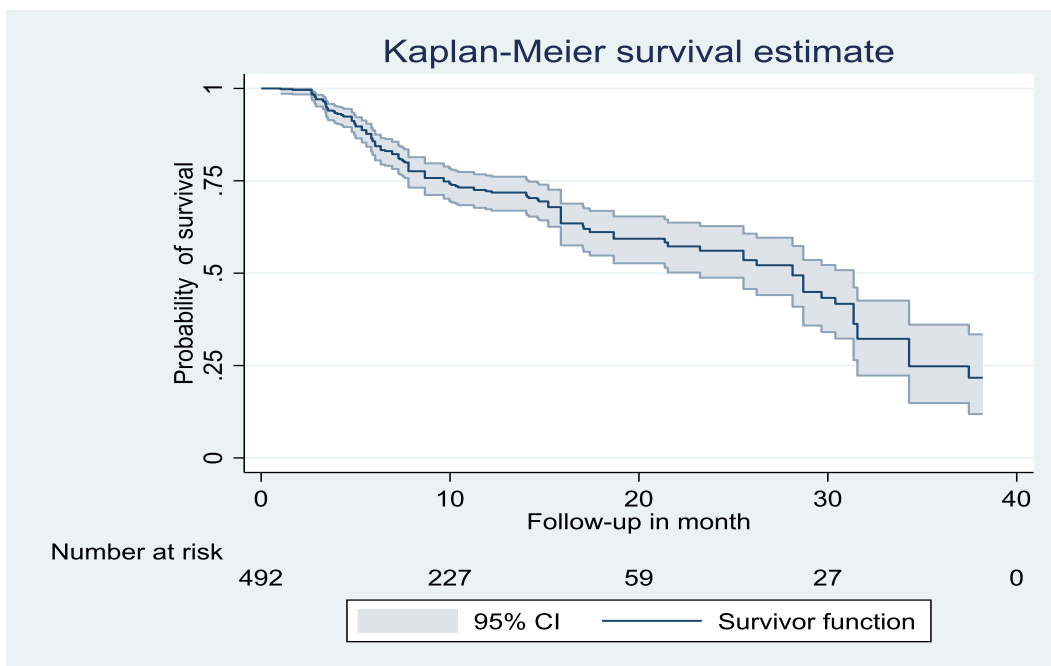


Figure 2).

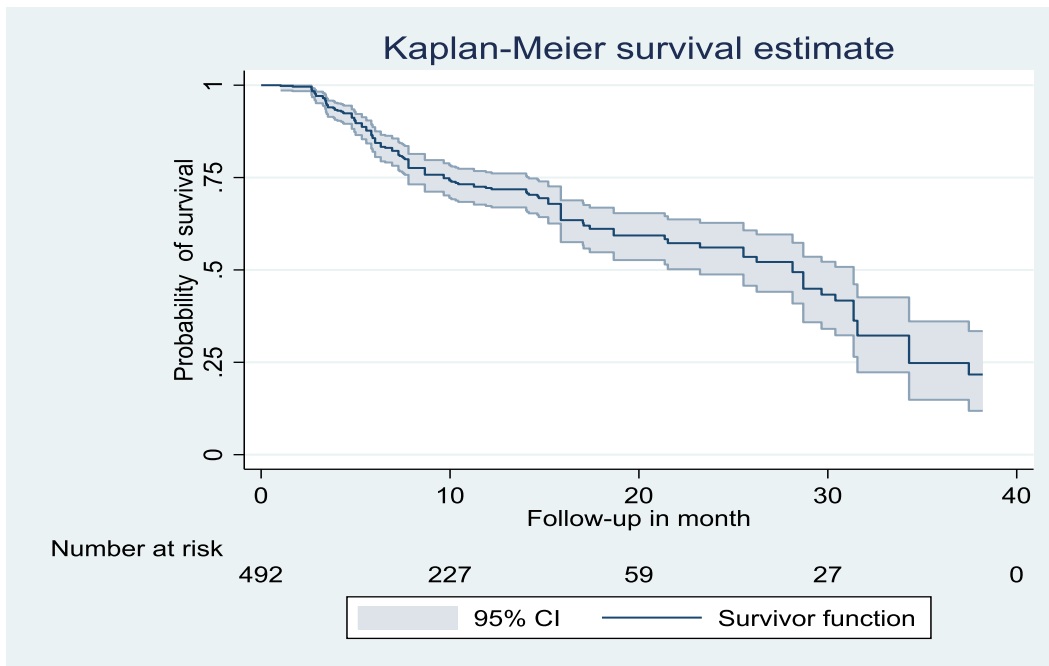


Figure 2 Plot of the overall estimate of Kaplan–Meier survivor function of breast cancer patients in Southern Ethiopia, 2023.

The incidence mortality for those who had started treatment at HUCSH was 3.1 per 100-person months; it was 3.7 per 100–person months for those who had started treatment at WSUCH.

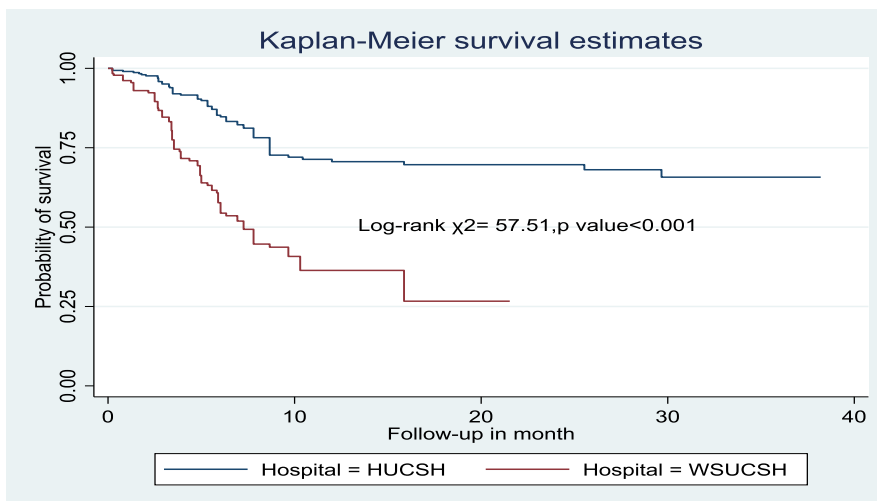


Figure 3 Kaplan-Meier survival estimate based on the breast cancer treatment center, Southern Ethiopia, 2023.

The incidence of mortality in BC patients with poor NPI was 5.6 per 100 person-months; it was 2.5 and 0.5 per 100 person-months for moderate and excellent NPI, respectively.

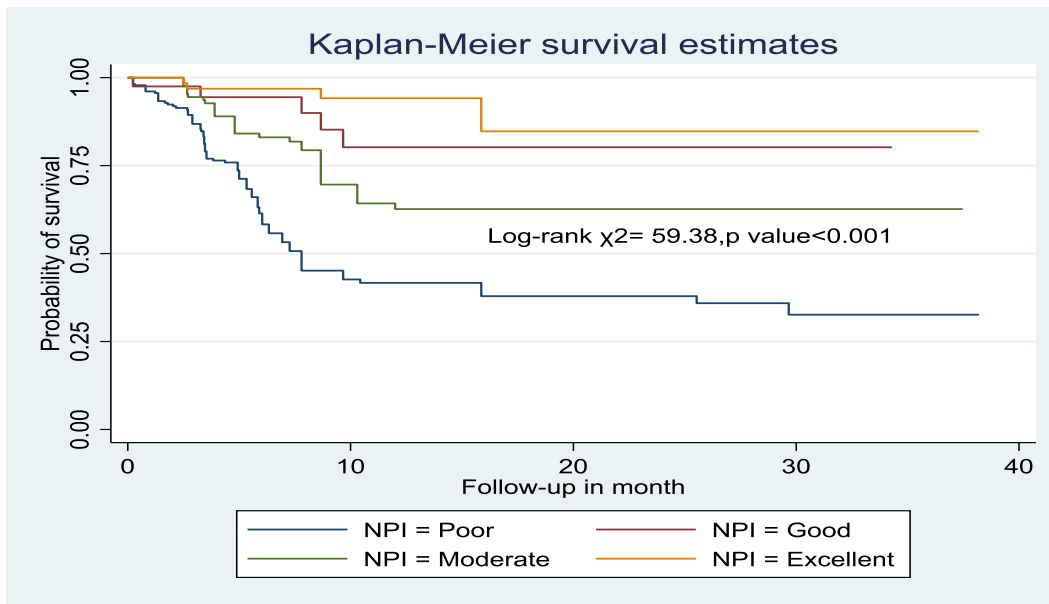


Figure 4 Kaplan-Meier survival estimate based on Nottingham prognostic index for breast cancer at Southern Ethiopia; 2023.

5.4 Prognostic Factors of Survival

In bi-variable parametric survival Weibull regression, age, menopausal status, deep surgical margin, hormone therapy, breast surgery, chemotherapy, residency, neutrophil-to-lymphocyte ratio, and NPI were found to be the prognostic factors of BC patients' survival. However, in the final multivariable model, the stage of BC, metastasis of BC, hormone therapy, chemotherapy, neutrophil-to-lymphocyte ratio, and NPI were significantly associated with the survival of BC patients.

Women who received chemotherapy had a 44% (AHR: 0.55, 95% CI: 0.33, 0.90) reduced risk of death compared to women who did not receive chemotherapy. For women with excellent and good NPI, the risk of death was decreased by 74% and 59%, respectively (AHR: 0.26, 95% CI: 0.12, 0.53) and (AHR: 0.39, 95% CI [0.18, 0.81]), as compared to women with poor Nottingham prognostic index. The risk of death was 1.73 (AHR: 1.73, 95% CI: 1.19, 2.51) times higher for women who had advanced BC than for women who had an early stage of the disease.

Similarly, women in BC who had metastasis had a 1.89 (AHR: 1.89, 95% CI: 1.31, 2.74) times increased risk of mortality than those who did not. Likewise, patients who had received endocrine therapy had 36% (AHR: 0.64, 95% CI: 0.44, 0.92) reduced hazards of death as compared to those women who had not received endocrine therapy. Furthermore,

women with lower neutrophil-to-lymphocyte ratios had 32% (AHR: 0.68; 95% CI: 0.47; 0.97) reduced mortality risks than those who had higher NLRs(**Table 3**).

Table 3: Bivariable and multivariable parametric Weibull regression analysis of predictive factors of breast cancer women in southern Ethiopia, 2023

Variables	Category	Survival status		CHR (95%CI)	AHR (95%CI)
		Event (n, %)	Censor (n, %)		
Age	<35 years	32(25.60)	93(74.40)	1	1
	35-50 years	83(31.09)	184(68.91)	1.30(0.86, 1.96) *	1.21(0.77, 1.89)
	>50 years	37(37.00)	63(63.00)	1.38(0.85,2.21) *	0.73(0.35,1.50)
Place of residence	Urban	64(31.68)	138(68.32)	1	
	Rural	88(30.34)	202(69.66)	1.10(0.80, 1.52)	
Menopausal status	Premenopausal	98(27.07)	264(72.93)	1	1
	Postmenopausal	54(41.54)	76(58.46)	1.30(0.92, 1.80) *	1.36(0.79, 2.34)
Educational status	Not attended formal education	59(42.75)	79(57.25)	1	1
	Primary	47(28.66)	117(71.34)	0.79(0.54, 1.16)	1.06(0.68, 1.66)
	Secondary	32(25.20)	95(74.80)	0.54(0.35, 0.84) *	0.83(0.51, 1.35)
	College and above	14(22.22)	49(77.78)	0.66(0.37, 1.20) *	0.81(0.43, 1.52)
Marital status	Married	103(29.10)	251(70.90)	1.13(0.80, 1.59)	
	Currently unmarried	49(35.51)	89(64.49)	1	
Stage of BC	Early	44(24.72)	134(75.28)	1	1
	Advanced	108(34.39)	206(65.61)	1.72(1.21, 2.44) *	1.73(1.19, 2.51)
NPI	Excellent	68(89.47)	8(10.53)	0.22(0.11, 0.44) *	0.26(0.12, 0.53) **
	Good	45(84.91)	8(15.09)	0.30(0.14, 0.63) *	0.39(0.18, 0.81) *
	Moderate	75(54.35)	63(45.65)	0.69(0.48, 1.01)	0.68(0.45, 1.02)
	Poor	95(42.22)	130(57.78)	1	1
NLR	≤3	90(27.52)	237(72.48)	0.67(0.48, 0.92) *	0.68(0.47, 0.97) *
	>3	62(37.58)	103(62.42)	1	1
Deep surgical margin	Free	97(28.70)	241(71.30)	1	1

	Involved	55(35.71)	99(64.29)	1.24(0.89,1.73) *	0.83(0.54, 1.26)
Histology of BC	Ductal	119(30.51)	271(69.49)	0.89(0.60,1.30)	
	Lobular	33(32.35)	69(67.65)	1	
Metastasis	Yes	94(37.15)	159(62.85)	1.93(1.39,2.69) *	1.89(1.31, 2.74) **
	No	58(24.27)	181(75.73)	1	1
Surgery	Yes	46(25.99)	131(74.01)	0.79(0.56,1.12) *	0.86(0.59, 1.24)
	No	106(33.65)	209(66.35)	1	1
Chemotherapy	Yes	122(29.26)	295(70.74)	0.62(0.41, 0.93) *	0.55(0.33, 0.90) *
	No	30(40.00)	45(60.00)	1	1
Waiting time	≤1month	60(28.57)	150(71.43)	1	
	>1month	92(32.62)	190(67.38)	1.03 (0.81, 1.30)	
Hormonal therapy	Yes	69(31.22)	152(68.78)	0.50(0.36,0.70) **	0.64(0.44, 0.92) *
	No	83(30.63)	188(69.37)	1	1

Note: * significant at a p-value <0.05 level and ** significant at a p-value <0.001 level: AHR; adjusted hazard ratio; BC: breast cancer; CHR: crude hazard ratio; NPI: Nottingham prognostic index; NLR: Neutrophil to lymphocyte ratio; currently unmarried (single, divorced and widowed)

CHAPTER VI

6.DISCUSSION

This study aimed to assess the survival status and prognostic factors among breast cancer women at selected hospitals in southern Ethiopia. In this study, the overall survival rate for breast cancer women was 54.5% at two years and 23.9% at three years. The Nottingham prognostic score, chemotherapy, educational and marital status, hormones, and neutrophil-to-lymphocyte ratio determined the prognosis of breast cancer women. The breast cancer patients' two-year survival rate was comparable to a previous study conducted in northwest Ethiopia, where BC patients had a two-year survival rate of 54.2% (12), and a study from western Ethiopia, which included patients without systemic treatment, demonstrated a two-year survival rate of 53% (29).

Though the finding was lower compared to the five-year survival rate reported from Sudan (58%) (10), China (64.42%) (42), Vietnam (74%) (3), Turkey (82.3%) (30), Iran (87%) (17), Brazil (87.3%) (35), France (87.6%) (37), and the United Arab Emirates (89%) (27). This discrepancy may be explained by the fact that breast cancer management requires the combination of various treatment modalities, but in this study, only 4.47% of patients received radiation therapy, and most of the patients delayed starting chemotherapy for more than a month, which reduced the probability of survival.

A further contributor might be that the majority of patients in Ethiopia delayed seeking medical attention and eventually presented with advanced stages of the disease, as well as a lack of knowledge and awareness of breast cancer, as well as the high cost of diagnostic procedures and treatments as well as misunderstandings about the illness, all of which together worsen BC patients' chances of survival (22, 43). This suggested that education campaigns regarding self-breast examination would encourage early case detection before progression and therefore increase their survival probability.

Consistency with existing evidence: the likelihood of breast cancer survival was higher for those women who had received chemotherapy. The risk of death was reduced by 45% for women who had received chemotherapy than those who had not received chemotherapy. This finding was consistent with other previous studies conducted in Ethiopia (44) and France (37). Adjuvant chemotherapy has been recognized as a primary systematic adjuvant

modality that affects grade III, hormone receptor+ (HoR+), human epidermal growth factor receptor 2+ (HER2+), HoR-/HER2+, and HoR-/HER2- molecular subtypes, respectively, and reduces the risk of local recurrence by half and increases the survival rate, particularly for T1b and T1c BC(36).

Endocrine therapy has also demonstrated a positive relationship with BC survival. Compared to BC women who did not receive endocrine therapy, those who had received it had a 36% reduced risk of death. The finding was similar to studies conducted at the University of Gondar Comprehensive Specialized Referral Hospital and in Brazil (31, 44). This can be explained by the fact that the use of adjuvant hormone therapy influences hormone receptors, women with estrogen-positive breast cancer were a reduced risk of death as compared to those who had estrogen-negative receptors (33).

A reduced probability of survival for BC women has been associated with the advanced stages of the disease. Women who presented with advanced stages of BC had a 1.73 times higher risk of death than women who had the disease at an earlier stage. The finding was supported by other studies conducted in Northwest Ethiopia, which reported that the advanced clinical stages of BC were associated with worsening clinical outcomes(12, 44). This could be explained by the fact that the women who presented with advanced BC are more likely to experience metastases to other organs, which has an impact on their survival.

The Nottingham prognostic index is one of the measures used to estimate the overall survival rate for patients with breast cancer(21). Women who had an excellent or good NPI had a higher survival rate compared to those who had advanced cancer or a poor NPI. This is because a BC woman who initially had a low NPI indicated that cancer had been detected early and that the patient had a good chance of surviving. This study also found that metastases were associated with a worse survival rate. Women in BC who had metastasis had about a two-fold increased risk of mortality compared to those who did not. The finding was similar to a study conducted in China and northern Brazil(18, 31).

Furthermore, the neutrophil-to-lymphocyte ratio is an important marker of tumor size, histology, and stages and could predict the survival of BC patients, particularly women with luminal breast cancer (45, 46). Women who had a lower NLR at the time of their BC diagnosis had a 32% reduced mortality risk compared to those who had a higher NLR. Similar findings were reported from China and Turkey: patients with a lower neutrophil-lymphocyte ratio (NLR) had an increased probability of overall survival (18, 30). This may be explained by the fact that an elevated neutrophil-to-lymphocyte ratio indicates advanced disease stages and is associated with a poor prognosis in breast cancer patients (45).

Limitations of the study

The findings of this study might suffer from the fact that it is a retrospective study based on records; some variables were missing, while others were not recordable. The study failed to track some deaths that occurred at home, and this may overestimate the survival rate because of the 11.5% of patients lost to follow-up that might be due to the complications of chemotherapy and are at high risk of death. Furthermore, due to the excluded records and the uncertain status of absconders, there may be a possible bias for some patients who were censored.

7. Conclusion

This study revealed that the breast cancer survivorship rate was lower than that of an earlier study from Ethiopia. About half the women presented with a higher NPI score and neutrophil-to-lymphocyte ratio; this suggested that the majority of women had been diagnosed at advanced stages of BC. The Nottingham prognostic score, chemotherapy, stages of BC, metastasis, hormonotherapy, and neutrophil-to-lymphocyte ratio determined the prognosis of breast cancer women.

8. Recommendations

Based on the finding the following recommendations were forwarded:

for women

- Women should improve their healthcare-seeking behavior, and practicing self-breast examination could help to downstage and promote early detection of cases before advancement can improve the survival rate.

for health professionals

- The early detection of breast cancer after visiting a healthcare facility should be emphasized by doctors as it significantly increases the likelihood that a woman will survive.

For hospitals

- It is desirable to start hormone receptor testing and radiation therapy in the hospital and ensure the accessibility and affordability of hormone therapy irrespective of receptor status, which is essential to improving survival time.

For the Federal Minister of Health

- The government should endeavor to increase public understanding of the benefits of early cancer detection and should also make it simpler for women to do so to reduce the risk of mortality.
- A regular breast cancer screening program in the community should be planned and implemented by the primary healthcare facilities since it will significantly decrease the risk of mortality.
- The government should equip the hospital with essential resources like mammograms, chemotherapy, and radiotherapy.

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ANNEXES

Annex I: INFORMATION SHEET

The title of the Research Project: Survival status and prognostic factors among breast cancer women in southern Ethiopia,2023.

Name of Investigator: Bitsiet Desta

Name of the Organization: Addis Ababa University college of health sciences and medicine, school of nursing

Name of the Sponsor: Wolaita Sodo university

Introduction: this information sheet is prepared for HawassaUniversity Comprehensive Specialized Hospital and Wolaita Sodo University Comprehensive Specialized Hospital, 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 study: The main aim of this study is to write a thesis as a partial requirement for the fulfilment of a master's degree in oncology nursing for the principal investigator. Moreover, the result of the study will be used as evidence and input for the hospitals and policy makers

Procedure: The data collectors will collect the necessary information from patient records using structured data extraction tools to have relevant data that is helpful for the study. The duration of data collection will be for 15 days.

Risk and /or Discomfort: Since the study will be conducted by taking relevant 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 is 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. The information retrieved will only be used for the study purpose.

Benefits: the research had no direct benefit for those whose document/ record is included in this research. But 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 patient with life threatening situation. Of all, the research work has a paramount direct benefit for health care planners and managers

Confidentiality: to reassure confidentiality the data on the cart will be collected by professional nurses who are working on clinic care area in the facility 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.

Contact address: This research project will be reviewed and approved by the ethical review board of college of health sciences and medicine of Addis Ababa university. If at any case you want to know more information about the research and its undertakings, you can contact the committee through the address of advisor and /or principal investigator.

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**ANNEX II: DECLARATION OF INFORMED VOLUNTARY
CONSENT:**

I have read the participant information sheet. I have clearly understood the purpose of the research, the procedures, the risks and benefits, issues of confidentiality, the right of participation and the contact address for any queries. I have been given the opportunity to ask any questions for things that may have been unclear. I was informed that I can terminate the study at any time. Therefore, I declare my voluntary consent to permit this study to be conducted in this institution with my signature as indicated below.

Signature of health facilities administrator_____

Name: _____ Date_____

Signature of Principal Investigator_____

Name: _____ Date_____

Thank you for your cooperation!!

Annex3:DATA EXTRACTION TOOL(questionnaire)

Part I: Socio demographic characteristics			remark
101	Identification number	-----	
102	Patient Age at diagnosis	-----year	
103	Place of residence	1.Urban 2. Rural	
104	Marital status	1.Single 2. Married 3.Widowed 4.Divorced	
105	Level of Education	1. No formal Education 2.Primary school 3.Secondary education 4. College and above	
106	Menopausal status	1.Premenopausal 2. Postmenopausal	
107	Pre-existing medical diseases at time of diagnosis (For a listing of condition, please refer to Annex III)	1.No 2.Yes 3.Unknown	
Part two: - clinical and histopathological variable			
201	Date of breast cancer diagnosis	-----/-----/-----	
202	Laterality	1.left 2.right 3.both side	
		1.clinically (physical exam, radiology) 2.cytology	

203	Basis of diagnosis Criteria	4.histology of metastasis 5.unknown	3.histology of primary
204	Primary site of breast cancer	2.upper inner quadrant 3.lower inner quadrant 4.upper outer quadrant 5.lower outer quadrant 6.axillary tail of breast 7.overlapping lesion and midline	1.nipple
205	Stage of cancer at diagnosis	1) I 2) II 3) III 4) IV	
206	Histological grades of breast cancer	1. well differentiated 2. moderately differentiated 3. poorly differentiated 4. undifferentiated 5.not determined	
207	Histology type of breast cancer	If Noninvasive carcinoma	1.Ductal carcinoma insitu 2.Lobular carcinoma insitu If Invasive carcinoma 1.Ductal 2.Lobular 3.Medullar
208	Deep surgical margin	1.	Involved

		2. Free/negative/	
209	Number of lymph nodes involved	-----	
210	Lymph Node status		1.positive 2.negative 9.missing
211	Tumor size in centimeter		-----
212	Cancer metastases at diagnosis		1.none 2.distance lymph node positive 3.distance metastasis not lymph node 4.contiguous extension from lymph to skin 5.distance lymph node and other metastases
213	Cancer metastases at diagnosis to bone	1.yes 2. no	
214	Cancer metastases at diagnosis to Brain	1.yes 2. no	
215	Cancer metastases at diagnosis to lung	1.yes 2. no	
216	Cancer metastases at diagnosis to liver	1.yes 2. no	
217	Estrogen receptor:		1. Negative 2. Positive 3. Not stated
218	Progesterone receptor:	1. Negative	

		2. Positive 3. Not stated	
219	Human epidermal growth factor receptor:	1. Negative 2. Positive 3. Not stated	
Part three: - Treatment related variable			
301	Date of starting treatment	-----year	
302	The primary treatment initiated	1. Radiotherapy _____ 2. Chemotherapy _____ 3. Radiotherapy & Chemotherapy _____ Surgery, Radiotherapy and chemotherapy _____ 5 Palliative care	
303	If chemotherapy	1. Regimen 2. how many cycles 3. Record total dose (or average) given for each cycle, by individual drug (units).	
304			

	If radiotherapy total dose of irradiation				
	Number of rounds				
305	If surgery was done: type of surgery	Partial mastectomy 1. (lumpectomy or quadrantectomy) Simple (total) 2. mastectomy Modified radical 3. mastectomy Radical 4. mastectomy Axillary node 5. dissection Other surgery---- 6. -----			
306	Was she on endocrine therapy? Hormonal	1. yes 2. no			
307	If yes please mention	1. drug type ----- 2. starting date _____ 3. total months of use-----			
308	Status of the patient during last contact	1. Death 2. alive 3. lost to follow up 4. transfer to another center 5. against medical advice			
309	If dead, lost to follow up, transfer to or alive when last date of contact	____/____/____			