Survival status and predictors of mortality among Breast cancer patients at Black lion specialized hospital, Adult oncology unit, Addis Ababa, Ethiopia, 2018. A retrospective follow-up study with survival analysis

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Abstract

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

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

Methods: An institution based retrospective longitudinal study was conducted in BLSH Adult Oncology Unit. All cases of breast cancer registered from January1st 2012-December30th, 2014 in BLSH were followed retrospectively for the six-year survival (until december30th, 2017). Kaplan-meier survival curve together with log rank test were used to test for the presence of difference in survival among predictor variables. Cox regression were used at 5% level of significance to determine the net effect of each explanatory variable on time to death after diagnosis of breast cancer.

Results: In this study incidence of mortality was 9.8 per 100 person years (95% CI: 8.49-11.47).The overall median survival time was 56.5(95% CI (53.46 - 60.83)) months. The overall estimated survival rate after diagnosis of breast cancer was nearly 27% (95% CI, 17.09 to 36.67 %) at 72 months of follow up. The overall survival rates at 1, 3, and 5 years were, 97.2%, 80.8%, and 46.2% respectively. Predictors of mortality were clinical stage (III&IV),(AHR =1.86), poorly differentiated histology (AHR: 3.1) & positive lymph node status (AHR:3.13).Whereas hormone therapy (AHR: 0.67),& chemotherapy (AHR:0.72) were protective.

Conclusion: The overall probability of survival was inferior when compared with those of high and middle-income countries. Significant predictors of mortality were advanced clinical stage, poorly differentiated histology grade, surgical margin involvement, positive lymph node status, Absence of hormone therapy, and breast conserving surgery. A special emphasis could be given to early screening; stage diagnosis & initiation of treatment.

Keywords:-Breastcancer,predictors**,**survival,Ethiopia

Introduction

Breast cancer is a leading cause of death worldwide, and ranks as the fifth cause of death among all forms of cancers, and which is the second most common cancer globally next to lung cancer and which accounts for 25% of cancer cases and 15% of cancer deaths among women worldwide(1,2). In US by 2017, an estimated 252,710 new cases of invasive and 63,410 new cases of non-invasive breast cancer and about 40,610 women were expected to die from the breast cancer.More than 1.1 million women globally are newly diagnosed and leads to 1.6% of worldwide female deaths annually from cancer causes(3,4). In less developed regions, breast cancer incidence was proportionally smaller, but it is the most frequent cause of death among women, whereas in more developed regions, mortality become decreased (5,6).The range in mortality rates with in developed regions is less than the incidence because of the more favorable survival of breast cancer in (high-incidence) developed regions(6).

Breast Cancer is an increasing public health problem for Sub- Saharan Africa at large (7).In Ethiopia, Breast cancer is the most prevalent cancer among women, and constitutes a major public health concern. Although, definite prevalence and incidence studies are lacking in Ethiopia, some estimates indicate that the breast cancer accounts for about 20.8 % of all cancers, which representing approximately 216 cases per annum (8).Breast cancer survival were varying greatly worldwide, ranging from 85% or higher (cumulative 5-year survival) in the high-income countries, while it is 60% or lower in many LMICs (9). Overall, in high-income countries, breast cancer is often diagnosed at an early stage and the prognosis is good; whereas in LMICs, women presents at a younger age, presents at a more advanced stage with more aggressive histologic characteristics ,and was associated with a worse survival (10,11).

The 5-year survival estimates of women having breast cancer in SSA revealed that near or below 50% in contrasting with 73% and 85% among black and white women in the US, respectively (7).Overall, LMICs had significant mortality rate than that of high-income countries. According to GLOBOCAN data, in 2012, the mortality/incidence ratios ranged from 0.55 in Central Africa to 0.16 in the U.S. As a result, mortality rates appear to be rising in certain LMICs, where as they decline in most high-income countries (12).Patients with late-stage disease had much lower survival rates than those with early-stage disease; patients with human epidermal growth factor receptor 2 (HER2) and triple-negative subtype tumors had lower survival rates (13).

According to World health organization estimation, an age standardize incidence case of breast cancer in Ethiopia were 12,956 and mortality rate of breast cancer were 25 per 100 000 women respectively(14) .As a result, to avert this burden currently the Ethiopian Federal Ministry of Health (FMOH) prepared a task force to address the issue of non-communicable diseases particularly with especial emphasis on cancer .One of the fundamentals parts of the strategic framework is to reduce the incidence and mortality of cancer and improve the quality of life of cancer patients (15). Despite the extensive knowledge about incidence and survival rates for cancer in the western world, cancer survival data is not widely available from countries in Africa, and Asia (16,17).Breast cancer is the most common cause of cancer deaths among women in developing countries particularly in SSA and survival tends to be poor in this region because of a combination of a late stage at diagnosis and limited access to timely and standard treatment(18) .Despite, the government concern on the issue of non-communicable diseases with especial emphasis on cancer, in order to reduce the incidence and mortality, the survival status of breast cancer patients still were not known in Ethiopia particularly at the BLSH. In line with the strategy, this study aimed to assess the survival status and its predictor of mortality among breast cancer patients at Black Lion specialized hospital, Addis Ababa, Ethiopia, 2018. Findings of this study could help to provide evidenced information to health authorities and other stakeholders in order to design interventions that can reduce the incidence and mortality of breast cancer.

Materials and Methods

Study design, setting and population

A six-year institution based, retrospective follow up study was conducted at BLSH. Patients who have been newly diagnosed and enrolled in breast cancer treatment, from January1st 2012 to December31th2014 at BLSH were followed until the end of the study (December 31th 2017). Black Lion specialized Hospital, is found in Addis Ababa, the capital of Ethiopia. It is a teaching; central tertiary comprehensive referral hospital has approximately more than 800 beds, give diagnostic, and treatment service for about 370,000-400,000 patients per year. The BLSH is the only specialized hospitals in the treatment of cancer in Ethiopia.

It has a number of services specialized in the treatment of cancers such as radiotherapy, medical oncology, anatomic pathology, nuclear medicine, gynecology and surgery. In BLSH oncology unit, there were three senior oncologists, one palliative care specialist, nine residents, five radiotherapist, four medical Physicist, and twenty-three nurses. The most common cancer cases seen in this hospital were breast, cervical, colon and sarcomas. This study was conducted at the oncology unit which is one of the specialty units of the hospital (19).

Inclusion and exclusion criteria

All adult breast cancer patients who were newly diagnosed and enrolled in BLSH during the required time (i.e. January1st 2012 to December31th2014) was included. Women, whose medical charts were incomplete, not found, those had previous diagnosis of breast cancer and a patient who had diagnosis at other hospitals and referred to the BLSH for further treatment was not included.

Sample size and sampling technique

All breast cancer patients who attended the oncology unit of BLSH from January1st, 2012 to December 31th, 2014 and fulfilled the inclusion criteria of the study was included in the study. This period was selected in order to have the nearest six year follow up study period. A total of 1,083 Breast cancer patient were registered in this period. Hence, 627 patients who fulfilled the inclusion criteria was included in the study. Finally, those who fulfill the criteria were used (**see figure1**).

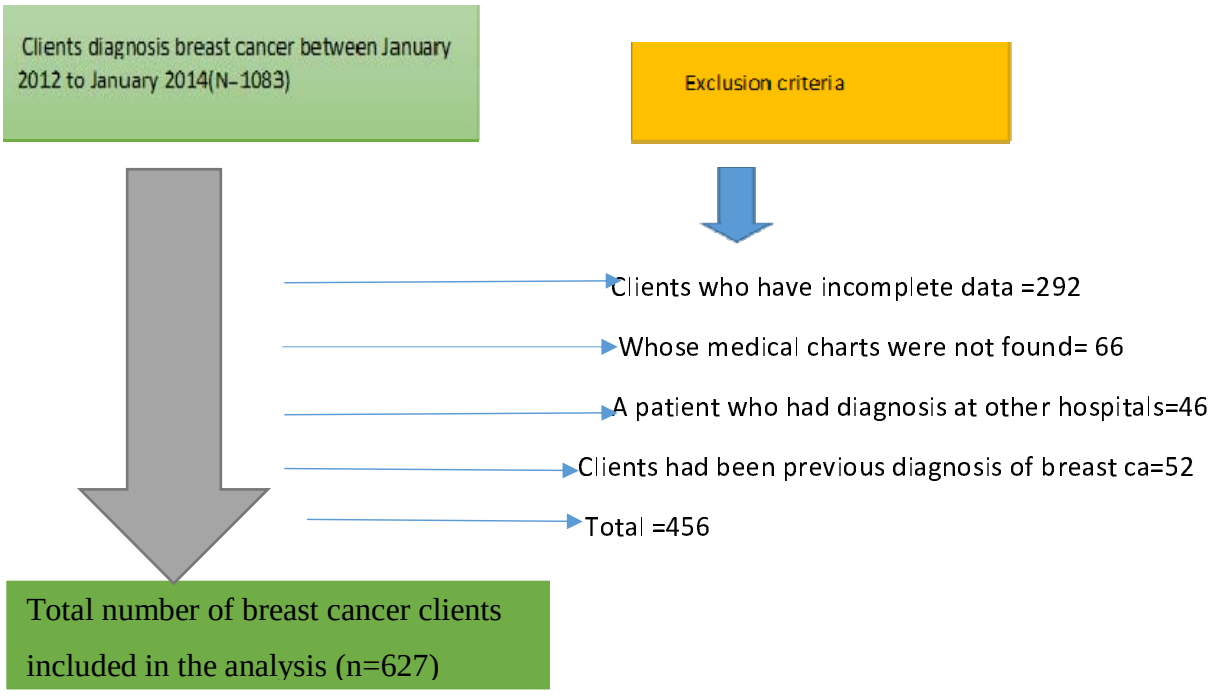


Figure 1:-flow diagram showing the final sample size included in the study at black lion specialized hospital, Addis Ababa, Ethiopia, 2018.

Data collection tool and procedure

A data abstraction format was develop from different literature. All available information on patient records were checked and formats from different literatures were reviewed with modification then appropriate data extraction format was adopted in English in order to extract all the relevant variables to meet the study objectives from patient charts. Training on record review was given to data collectors and supervisors for 01 days before actual data collection task on the already existing records half-day theoretical and half-day practical training. The starting point for retrospective follow-up was the time from first confirmed diagnosis of breast cancer and the endpoint was date of death, date of lost to follow up, date of last contact until January 31th, 2017.

All Socodemographic, clinical, pathological and treatment data were obtained from medical reports of all breast cancer cases diagnosed from January 1st 2012 to December 31th 2014 at BLSH was reviewed from cancer registries. The record of all study participants were select according to the eligibility criteria. The survival status of patients were obtained from the medical record. Survival time was calculate as the time between the date of diagnosis of breast cancer to the date of death, or the end of study. Before collecting the data, the records were reviewed (both baseline and follow up records), death certificate complemented by registration was identified from their medical record number. Then, three oncology nurses who were working at the cancer treatment center extracted and reviewed the charts.

Definition and measurement of variables

Age at diagnosis was categorized into four groups (<40,40-49,50-59,>60+ years), according to the American Cancer Society fact and figure for breast cancer. Comorbidity conditions was taken from the Charlson index that have been used in the breast cancer survival literature (20,21). The presence of any of these conditions at diagnosis was designate a „yes□, while the absence of these condition at diagnosis was denoted as no. Menopausal status (premenopausal/postmenopausal), marriage status (single, married, widowed, divorced), place of residence (urban/rural).

Clinical stage at diagnosis was assigned to each patient by using the American Joint Committee on Cancer TNM classification scheme for staging breast cancers was used (17).In this research, the coding for those diagnosed at stages I and IV remained. Stages IIA and IIB were collapsed as stage II, and stages IIIA, IIIB and IIIC were collapsed as stage III. All staging information mentioned within the first 3 months after primary diagnosis were used. Histological grade of breast cancer was assessed by the Nottingham Grading System, grade (1-well differentiated / 2 moderately differentiated / 3-poorly differentiated). Tumor size was categorized in accordance with American Joint Committee on Cancer (AJCC) guidelines (≤2 cm, >2–5 cm, >5cm), margins (clear/involved), axillary node status (positive/negative)**,** Hormonal therapy (yes/no), histology type (ductal insitu, ductal invasive, lobular insitu, lobular Invasive), were also recorded. The first course of treatment was classified as chemotherapy associated with surgery (including breast-conserving and mastectomy in addition to sentinel node biopsy or complete axillary dissection) and radiotherapy, surgery alone and surgery associated with radiotherapy. The time (measured in months) to the death was used for the survival analysis.

Outcome variable

The primary outcome variable was time to event in months. Breast cancer patients were followed until the date of death, loss to follow-up, transferring out, or the end of the study. Individuals who were lost to follow-up, alive and had transferred out at the end of the study period were censored. The survival time was calculated in months using the time between the dates of diagnosis and the date of the event (death) or date of censoring.

Data entry and analysis

Data was coded and then, cleaned, entered, edited using EPI-data 3.1 and transferred to STATA 14 statistical software for analysis .Data exploration was undertaken to see if there are odd codes or items that were not logical and then subsequent editing was made. Summary statistics were carried out to describe the demographics, clinical and follow up data in terms of central tendency and dispersion value for continuous data and frequency distribution for categorical data. Incidence density rate (IDR) was calculated for the entire study period. Subsequently, the number of mortality within the follow up was divided by the total person time at risk on follow up and reported per 100PY. Kaplan-Meier survival curve together with log rank test were used to test for the presence of difference in survival among categories of covariates and log rank

test was used to compare survival curves. Before running the Cox regression model assumption of proportional-hazard and multi-colinearity were checked. Lastly, the outcome of each subject was dichotomized into censored or death.

Bivariable cox regression was first fitted and those independent variables, which become significant on the bivariate regression having p-value ≤ 0.25 level of significance, were included in the multivariable analysis. Cox proportional-hazard regression was fitted at 5% level of significance to determine the net effect of each explanatory variable on time to death after diagnosis of breast cancer. Cox-proportional hazard model assumption was checked using schoenfeld residual test and variables having P-value >0.05 were considered as fulfilling the assumption. Residuals were checked using goodness-of-fit test by Cox Snell residuals, which is, satisfied the model test.

Result

Socio-demographic characteristics of the study participants

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

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

Covariate	category	Vital status at last contact		Total No. (%)
		Censored No. (%)	Death No. (%)	
Age in years at timeof diagnosis	<40	212(75.9)	67(24.1)	279(44.49)
	40-49	111(68.09)	52(31.91)	163(26.0)
	50-59	93(78.81)	25(21.19)	118(18.82)
	>60+	42(62.28)	25(37.31)	67(10.68)
Placeof residence	Urban	285(77.86)	81(22.14)	366(58.37)
	Rural	173(66.28)	88(33.71)	261(41.63)
Marital status	Single	71(76.34)	22(23.66)	93(4.83)
	Married	301(74.68)	102(25.32)	403(64.27)
	Divorced	63(63.64)	36(36.36)	99(15.78)
	Widowed	23(71.87)	9(28.13)	32(5.1)
Menopause status	Premenopausal	316(72.97)	117(27.03)	433(69.05)
	Postmenopausal	142(73.19)	52(26.81)	194(30.95)
Preexisting medical diagnosis	No	323(80.14)	80(19.86)	403(64.27)
	Yes	135(60.26)	89(39.74)	224(35.73)

Clinical, histopathological and treatment characteristics

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

modified radical mastectomy surgery. The Clinical, histopathological and treatment characteristics of the study participants are shown below(**Table 2**).

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

Variable	**Category**	**Vital status at last contact**		**Total**
		Censored No.(%)	death No.(%)	**No.(%)**
Stage of breast cancer	I	21(95.45)	1(4.55)	22(3.5)
	II	145(86.82)	22(13.18)	167(26.63)
	III	245(68.62)	112(31.38)	357(56.93)
	IV	47(58.02)	34(41.98)	81(12.91)
Histology grade	Grade I	84(91.3)	8(8.7)	92(14.67)
	Grade II	237(77.96)	67(22.04)	304(48.48)
	Grade III	137(59.3)	94(40.7)	231(36.84)
Histology type	Ductal insitu	136(83.44)	27(16.56)	163(26.3)
	Invasive ductal	294(68.85)	133(31.15)	427(68.1)
	Lobular insitu	15(75)	5(25)	20(3.2)
	Invasive lobular	11(73.4)	4(26.6)	15(2.4)
Deep surgical margin	Free	393(80.2)	97(19.8)	490(79.28)
	involved	58(45.3)	70(54.7)	128(20.72)
Node status	Negative	364(80)	91(20)	455(72.68)
	Positive	93(54.38)	78(45.62)	171(27.32)
Metastasis at time diagnosis	No	348(87.21)	51(12.79)	399(63.64)
	Yes	110(48.24)	118(51.76)	228(36.36)
Tumor size	≤2.5cm	289 (81.17)	67(18.82)	356(56.78)
	2-5cm	152(63.34)	88(36.66)	240(38.27)
	>5cm	17(54.8)	14(45.2)	31 (4.95)
Number of Positive node	<2	284(75.53)	92(24.47)	376(59.97)
	>=2	174(69.32)	77(30.68)	251(40.03)

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

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

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

Survival status of breast cancer patients

The overall mortality rate in the cohort during the 1,712 person-years of observation (PYO) was 9.87 per 100 (95% CI: 8.49- 11.47) person-years follow up. The cumulative incidence of this study was 169(27%) with the confidence interval (95%CI, 23.6-30.3%) of patients were died over six years. However, 458 (73.04%) were censored till the end of the study. Of these, 194(42.27%) were lost to follow up, 132(28.76%) were alive 119(25.9%) was against medical advice and the rest were transfer to other institution at the end of the follow up.

Overall Survival Function of breast cancer patients

In the present study, 627 breast cancer patients were followed up for a total of 72 months, with a median survival time of 56.5(95% CI, 53.46 - 60.83) months. Kaplan-Meier survival estimation showed that overall estimated survival rate after diagnosis of breast cancer was 26.42% (95% CI, 17.09 to 36.67 %) at 72 months of follow up. The estimated cumulative survival was 97.2%, 89.8%, 80.8%, 66.33%, 46.2% and 26.4% at 12, 24, 36, 48, 60 and 72 months respectively **(see Figure 2)**.

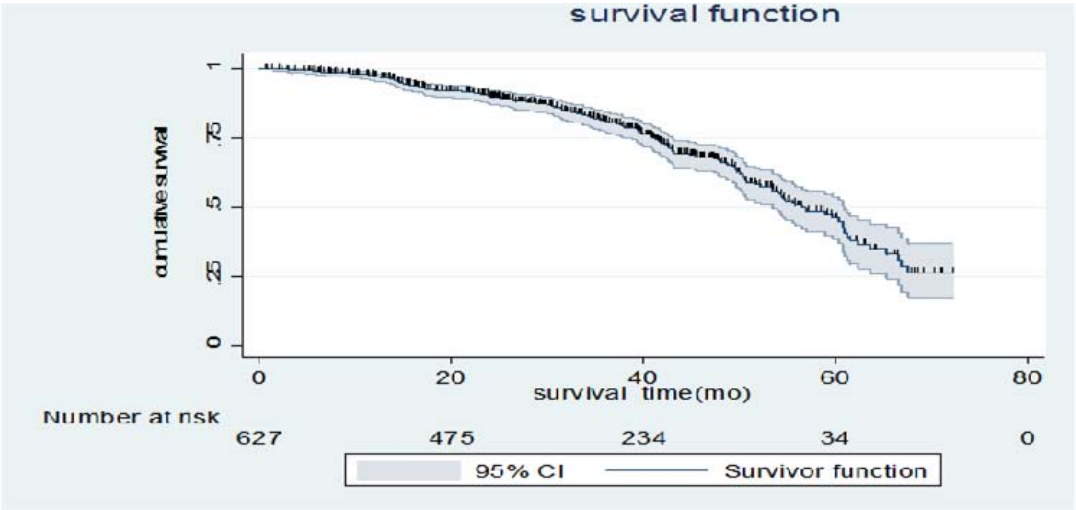


Figure 2.Summary of Kaplan Meir survival estimate on the survival time of breast cancer patients in Black lion specialized hospital, Addis Ababa, Ethiopia, March - April, 2018 (n = 627).

Survival function among different groups of Breast cancer patients

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

Among 189(30.14 %) cases diagnosed in early stage (I&II), cumulative survival was 56.65% (95%CI: 35.94-72.94%), while, those cases diagnosed at advanced stage (III&IV), 438(69.86%) had a survival rate of 18.49% (95%CI: 10.03-28.98%). Which shows Breast cancer mortality was correlated to the stage at diagnosis and testing equality among the groups with p value of 0.000. A 6-year survival for histological types indicated that, there was a

significant difference in survival rates of 20.2% (95%CI,10.82-30%) for those diagnosed with IDC (invasive ductal carcinoma) as compared to other breast cancer types 43.26%(22.39-62.56) (**table 3 and figure 3**).

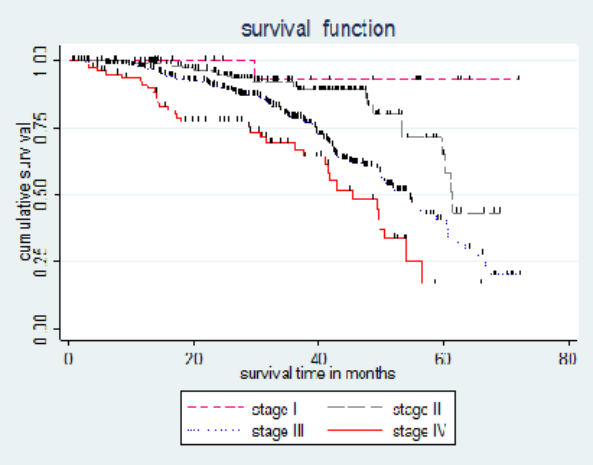
Table 3:-Survival time, cumulative survival probability, significance and log rank test for the study population according to different characteristics of patients during 6-year of follow-up (Kaplan-Meier method) of breast cancer patients at, black lion specialized hospital, Ethiopia from January 1st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

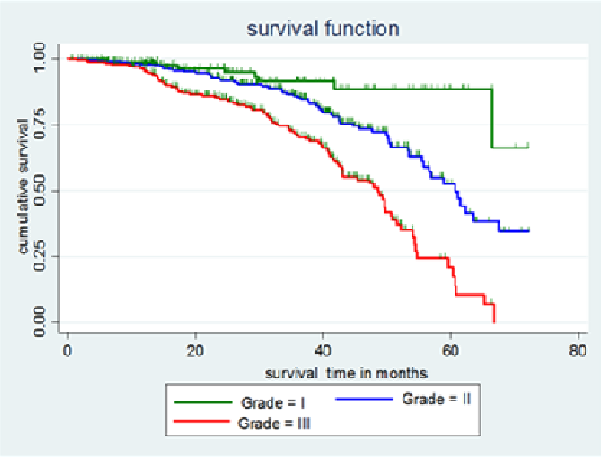
Covariate	Survival time, mo, (95% CI)		Overall 6-year survival (%)	Log rank tes (p–value)
	Mean (95% CI)	Median(95%CI)		
Residence				
Urban	55.6(52.8-58.30)	59.7(54.47-..)	36.57	
Rural	49.2(46.25-52.2)	50.73(49.3 -60.67)	17.26	(8.83) *
Menopause status				
Premenopausal	53.4(50.88- 55.8)	60.7(53.47-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

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

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

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





A B

Figure 3. Kaplan-Meier Survival function among different groups of Breast cancer patients by stage at diagnosis (A), histologic grade at diagnosis(B), at Black lion Specialized hospital,Addia Ababa, Ethiopia, 2018 (n=627).

Testing overall model fit

This figure shows if the cox regression model fits the data, these residuals should have a standard censored exponential distribution with hazard ratio. If we comparing the jagged line with the reference line, we observe that, the Cox model does fit these data to reasonable. The hazard function follows the 45° line very closely .Hence, the output shows cox–snell residuals were satisfied the overall model fitness test (**see figure 4**).

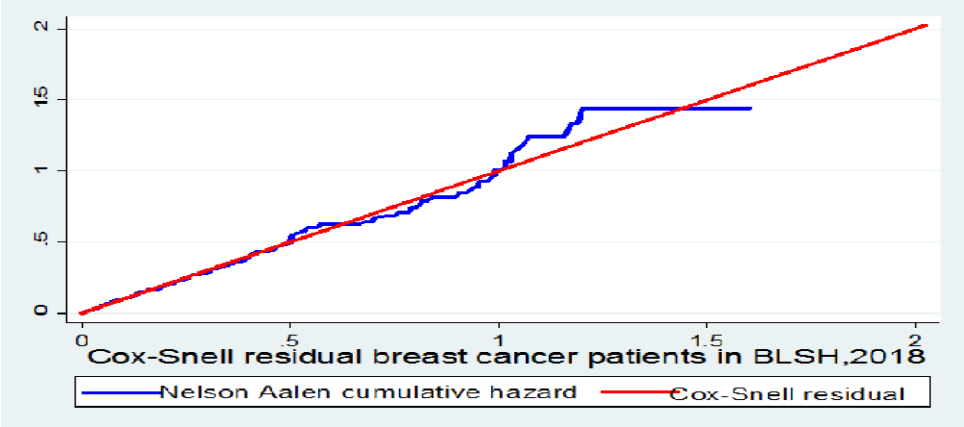


Figure 4 .Cox-Snell residual Nelson -Aalen cumulative hazard graph on breast cancer patients in Black lion specialized hospital, Addis Ababa, Ethiopia, March- April 2018.

Predictors of mortality

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

In multivariate Cox regression analysis those variables with p-value <0.25 in the bivariate analysis and non-collinear independent variables were included. In multivariable cox proportional hazards model, seven variables were associated with breast cancer mortality. The

result of multivariable analysis revealed that women with advanced clinical stage (III and IV) were 1.86 times more likely to die as compared to those with early clinical stage (I and II) (AHR : 1.86, 95%CI: 1.127- 3.080). Those women whose surgical margin involved at baseline were 3.13 times more likely to die as compared to those women whose surgical margin was not involved (AHR: 3.13, 95% CI: 2.140- 4.573).

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

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

Characteristics	Bivariable cHR (95% CI)	Multivariable aHR (95% CI)
Age		
<40	1	1
40-49	1.45(1.010-2.089)*	1.21(.766- 1.898)
50-59	1.21(0.761-1.919)	0.88(0.468- 1.660)
>60+	1.84(1.080-3.141)*	1.62(0.766- 3.447)
Place of residence		
Urban	1	1
Rural	1.57(1.164-2.130)*	1.48(0.999-2.195)
Marital status		
Married	1	1
Single	1.07(.708- 1.629)	0.95(0.551- 1.638)
Widowed	1.77(1.224- 2.568)*	0.69(0.395- 1.224)
Divorced	1.34(0.826- 2.363)	0.67(0.318 -1.422)
comorbidity		
no	1	1
yes	2.07(1.530- 2.808)*	1.49(0.980- 2.290)
Stage of breast cancer		
Early (I&II)	1	1
Advanced (III&IV)	3.11(2.01-4.84)*	1.86(1.127-3.080)**

Histology grade		
Grade I	1	1
Grade II	2.92(1.40-6.09)*	1.73(0.67-4.53)
Grade III	6.79(3.28-14.06)*	3.12(1.16-8.36)**
Histology type		
Invasive Ductal	1.87(1.298-2.714)*	1.04(0.644- 1.697)
Others	1	1
Surgical margin involved		
No	1	1
Yes	3.06(2.252-4.168)*	3.13(2.140- 4.573)**
No of involved lymph node		
<2	1	1
>=2	1.34(0.991-1.822)	0 .79(0.517- 1.205)
Lymph node status		
Negative	1	1
Positive	1.61(1.396-1.848)*	1.83(1.217- 2.736)**
Tumor size		
≤2.5	1	1
2-5	2.19(1.593-3.021)*	1.15(0.736- 1.832)
>5	2.08(1.172-3.717)*	2.31(0.891-4.123)
Type of surgery		
Partial mastectomy	1	1
Simple (total) mastectomy	0.61(0.378- 0 .986)	0 .68(0.413- 1.134)
MRM	0.48(0.318-0.714)*	0.45(0.280- 0 .690)**
Axillary node dissection	1.51(0.735-3.084)	1.25(0.593- 2.660)
Radiotherapy		
No	1	1
Yes	0.79(0.586-1.074)	0.95(0.654- 1.381)
Chemotherapy		
No	1	1
Yes	0.72(0.467-1.099)	0.27(0.130-0.565)**
Hormone therapy		
No	1	1
Yes	0.38(0.281-0.519)*	0.67(0.451-0.989)**

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

Discussion

A retrospective follow up study was carried out among breast cancer patients at BLSH in Ethiopia. This study aimed to asses' survival status and predictors of mortality among breast

cancer patients. In the current study, the overall mortality rate of breast cancer patients during 72 months follow up were 9.8/100 women- years. This finding is much higher than what was reported in a study in Brazil (22), where age-standardized breast cancer mortality rate within 6-year follow up period of 431.8 /100 000 women-years was found. The observed difference in mortality rates may be due to, the fact that more advanced stage (III$IV) breast cancer were presented in our finding. Other possible explanation could be methodology difference; they have been used ecological analysis.

In this 6-year retrospective follow up study, the overall survival rates at 1, 3, and 5 years were, 97.2%, 80.8%, and 46.2% respectively. This finding is consistent with other previous studies which have been conducted in Malaysia (70.8%, 56.9% and 49.4%) (23) and Ghana, (47.9%)(17) .However, this finding is higher than those in other African countries in Tanzania (21.8%) (24) and Cameroon (30%) (25) at 5 years and even lower than previous results in Uganda (51.8 %) (26), and Vietnam, (94%, 83% and 74%)(4).This ,figure is still lower when compared with that of studies of high income countries such as Northwest Iran (96%, 86%, and 81%), Germany(83%),and the Qidong(83.61%,67.53%,and58.75%)respectively (27-29). Similarly, the overall cumulative 6 years estimated survival rate of the current study was 26.42% (95% CI: 17.09-36.67 %) at 72 months of follow up. This, finding is lower than the study done in Qidong (56.04%) (29).

This gap might be due to several reasons. This perhaps could be due to advanced stage at diagnosis in ours (69.5%). However, 52.3% in Ghana, 27.6% in Vietnam, 67.8% in Cameroon, lack of early screening programs, limited treatment facilities, and financial problems. Other explanation could be the facilities to treat cancer are located in the capital city of the country; hence, most cancer patients were referred to the central level this could result delay in diagnosis and treatment. Additional, possible explanation variations in survival could be due to different methodologies applied in each of the studies but also to different sample compositions regarding stage, age, and other biologic tumor factors, as well as differences in local cancer care. Furthermore, the molecular and genetic differences in breast cancer may also contribute to geographic variations in survival.

In our study, the overall median survival for histologically confirmed breast cancer was 56.5(95% CI, 53.46 - 60.83) months. Our results were higher than the previous studies in which the median survival was 24 months in Cameroon (25),40 months in Sudan (30) ,but lower than

to the result reported from Malaysia the median survival was 68.1 months(23). Although, our study showed higher overall median survival than that seen in the Cameroon and Sudan studies, the lower value obtained in comparison with Malaysia is most probably due to shorter period of study in ours. In addition, it could be difference in health seeking behaviour and treatment adherence among those studies.

In the log rank test it is found that there is a significant difference in survival experience between different baseline characteristic of breast cancer patients. To test the equality of survival curve Kaplan-Meier analysis of survival status showed that the median survival time for those who had clinical stage I, II or III at baseline had a longer survival time than those in advance clinical stage (IV) (45.6 months, 95% :41.04- 50.57) this difference was statistically significant with p-value < 0.000. Similarly, the median survival time for those who have negative lymph node status had a longer survival time was (63.6month, 95%CI: 60.67- ..) than those who had positive lymph node at baseline (47.34months, 95% CI: 41.2-49.7). This finding is in line with study done in African countries (30,31).

In the present study, lymph node status was found to be an independent predictor of mortality among breast cancer women. Women who had positive lymph node at diagnosis were nearly 2 times higher risk of death as compared to women who had negative lymph node at baseline. This finding is in agreement with different studies conducted in African countries (17,32) ,and also in the study done in Iran (33) ,in which lymph node status was an important determinant of survival. Despite being positive lymph node status, as the number of involved lymph nodes increases, so does the relapse rate, while the survival rate decreases. In the current study, histologic grade found to be an independent predictor of mortality. Women who had histologic grade III at diagnosis were nearly 3 times higher risk of death as compared to women who had well differentiated histologic (grade I) at baseline. This finding is in line with other previous studies which have been conducted in Asian countries (23,33,34).

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

with surgical margin free (4,26).which reflect surgical margin was an important determinant of survival. Such findings could be explained by the fact that residual disease at the surgical margins could increase the risk of local recurrence and possibly death through the years

As shown by others, we found that advanced clinical stage (III and IV) was found to be a strong marker of mortality among breast cancer women. Women who had clinical stage (III and IV) at diagnosis were nearly 2 times higher risk of death as compared to women who had clinical stage (I$II) at time of diagnosis. This finding is in agreement with several studies conducted in different Africa and Asian countries (4,26, 28,34). Stage is an important predictor of survival from breast cancer, and the most significant influence on patient outcome in the present study.

The result from this study shows patients who had undergone modified radical mastectomy (MRM) was found to be a predictor of prolonged survival and reduced incidence of death AHR, 0.45(0.280- 0 .690).That is women who were operated MRM had 55% more chance of surviving than those who did undergone lumpectomy(breast conserving surgery) at any time. This finding is in contrary with studies done in different Africa and Asian countries (25,27,33).Which identified breast-conserving surgery, have better survival than mastectomy. The difference in survival a mong two groups could be because of advanced stages at presentation and poor infrastructure for treatment of breast cancer have made this mode of surgical treatment more popular in many developing countries including Ethiopia. Scientifically, breast-conserving surgery is usually indicated for early breast cancer in contrast to modified radical mastectomy whose indications also include advanced stage disease. Other possible explanation could be the options for treating a patient with breast cancer depends on the stage of disease.

Unlike most of previous findings (31,36) chemotherapy was found to be an independent predictors of survival that becomes statistically significant in the cox proportional hazard model. Those women who had receiving chemotherapy was significantly predictor to reduced incidence of death, AHR 0.27 (95%CI: 0.130- 0.565) patients without chemotherapy had 27% more chance of death than that of patients who was treated. However, this finding is in line with study done in France (37),which exhibited a 25% reduction in the relative risk of death compared with the untreated group (HR = 0.75 [0.69–0.83], p<0.0001).Generally, our study found a positive effect of chemotherapy on survival for breast cancer patients. Those who had

taken chemotherapy, lower the risk of death due to breast cancer. This might be due to patients with advanced stage breast cancer, chemotherapy may be, applied in order to shrink the tumor size and facilitate surgery. In addition, chemotherapy may be, given after surgery in order to reduce the risk of recurrence arising from residual disease. For patients in our study, the better survival rate was related to patients receiving chemotherapy. Additional studies should be conduct to confirm a positive impact of chemotherapy on survival rate of breast cancer.

The final predictor of survival found in the study was hormone therapy within a 6-year treatment course. This therapy reduced the risk of death among breast cancer patients in the study population. The finding is consistent with previous findings in many studies all over the world (4,31,36).Where, hormone therapy was found to have a protective effect for mortality (AHR, 0.67; 95% CI, 0.451- 0.989). The effect of hormone therapy on survival improvement was often mentioned along with the influence of hormone receptors.

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

Conclusion

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

reduced mortality. Hence, a special emphasis should be given to early screening, diagnosis & initiation of treatment since advanced stage were prone to high mortality.

Ethics approval and consent to participate

Ethical clearance was obtained from Addis Ababa University, College of Health Sciences, and school of nursing and midwifery Ethical review board. Permission for conducting the study was obtained from black lion specialized hospital adult oncology unit. As the study was conduct through review of medical records, the individual patients were not subjected to any harm as far as the confidentiality was kept. To keep the confidentiality all collected data was coded and locked in a separate room before entered into the computer

Consent for publication

Not applicable.

Availability of data and materials

Data will be shared up on request and will be obtained by emailing to the corresponding author using “wshibabaw2015@gmail.com”.

Abbreviations

AAU=Addis Ababa University,AJCC=American joint committee on cancer, BLSH=black lion specialized hospital,ER=estrogen receptor,EFMOH= Ethiopian federal ministry of health, GLOBOCAN=global burden of cancer,HER2= Human epidermal growth factor receptor 2,HIC=high income country, IDC=invasive ductal carcinoma,LMICs=low and middle income countries,PR= progesterone receptor,SSA=sub-Saharan Africa.

Competing interest

The authors declared that, we have no any competing interest

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Authors' contributions

Conceptualization: WS

Formal analysis: WS.

Funding acquisition: WS.

Investigation: ET TK.

Methodology: HA WS TM.

Software: TY WS YA

Supervision: WS YA

Writing – original draft: WS HA TM.

Writing – review& editing: WS HA TM YA TY.

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