THE UNIVERSITY OF NAIROBI INSTITUTE OF TROPICAL AND INFECTIOUS DISEASES

SCHOOL OF HEALTH SCIENCES

CLINICAL OUTCOMES OF HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 NEU POSITIVE BREAST CANCER PATIENTS AT AGA KHAN UNIVERSITY HOSPITAL, NAIROBI; A SURVIVAL ANALYSIS STUDY

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICAL STATISTICS.

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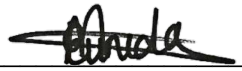
DECLARATION

This thesis is my original work and has not been presented for a degree in any other University.

Signature  Date 22nd Nov 2019

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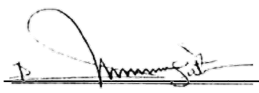
Signature  Date 22nd Nov 2019

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DEDICATION

I dedicate this dissertation to my friends and family who have supported me throughout the process. I will always appreciate all they have done to make me achieve my dreams.

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ABBREVIATIONS AND ACRONYMS

AKUHN	Aga Khan University Hospital Nairobi
ASCO	American Society of Clinical Oncology
BCSS	Breast Cancer Specific Survival
CI	Confidence Interval
DDFS	Distant Disease Free Survival
DFS	Disease Free Survival
FISH	Fluorescence Insitu Hybridization
GHEA	Group Trastuzumab in Adjuvant Therapy
HER 2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
IDFS	Invasive Disease Free Survival
IHC	Immunohistochemical Analysis
NCCN	National Comprehensive Cancer Network
OS	Overall Survival
RFI	Recurrence Free Interval
RFS	Recurrence Free Survival
RFS	Relapse Free Survival
RR	Relapse Rate
SEER	Surveillance, Epidemiology & End Results Programme
TNBC	Triple Negative Breast Cancer
WHO	World Health organization.

OPERATIONAL DEFINITION OF TERMS

Adjuvant therapy	Treatment of cancer given after primary treatment to decrease the risk of the disease coming. Examples include chemotherapy, hormonal therapy, radiation therapy, or biological therapy.
Clinical stage	The stage that shows how cancer has spread in the body which is determined by tests done prior to surgery. The tests are blood tests, imaging, and biopsies.
Early stage breast cancer	Cancer of the breast which has not spread past the breast or past lymph nodes of the axillary. This stages are stage IIA, stage IIB, and Stage IIIA breast cancers.
Neoadjuvant	First treatment given to shrink the tumour just before main treatment is given and is normally surgery.
Pathological stage	The spread of cancer in the body which is determined microscopically and is based on how different the cells are from the normal cells in a tissue sample.
Tumour grade	Pathological description of a tumour looking at the abnormality of the tumour cells and tumour tissue under the microscope.

ABSTRACT

Worldwide, breast cancer in women is ranked as second and most common type of cancer. Also, known to be the most common cause of mortality in women population in less developed regions. Up to 25.6% of breast cancer patients in Kenya are diagnosed as having HER 2 positive disease according to Triple Negative Breast Cancer (TNBC) study that was conducted between 2012 to 2017. Adjuvant therapy reduces recurrence and mortality risks by 1/2 and 1/3 respectively, in early breast cancer stage, but the costs for one year of trastuzumab range from $70,000-$110,000 which is much high hence unaffordable for most of the patients in sub-Saharan Africa many of whom have to pay out of pocket for the drug . The aim of the study was to determine survival outcome of HER-2 Neu positive early breast cancer patients diagnosed and treated at Aga Khan University between 2012 and 2017 who received primary therapy (Neoadjuvant) and adjuvant treatment and those who got adjuvant chemotherapy plus trastuzumab. A retrospective cohort design which included HER2-positive, consecutive early breast cancer patients treated in adjuvant setting in routine practice in Aga khan University Hospital from 2012 to 2017. Analysis was done on 83 cases which had all the parameters of interest out of the 166 that were positive for Her-2 receptor status. The associations of patient tumour and socio demographic characteristics with predefined survival outcomes were analyzed using STATA version 15. 83 patients were diagnosed with HER2-positive early breast cancer disease, out of which 32 received adjuvant therapy alone and 34 received adjuvant plus Her 2 blockade. Results showed overall survival outcomes in Her-2 positive early breast cancer patients who received Trastuzumab in addition to neo-adjuvant and adjuvant therapy were not statistically different using Log-rank test (P-value=0.172. The unemployed patients had 6.23 higher hazard of death compared to those who were self-employed (CI 1.33-29.28; P.value-0.020). Patients with tertiary education had 91% rate of overall as compared to the primary level of education with (CI 0.02-0.04, P-0.03). Procedures for cancer treatment should be standardized across all hospitals in Kenya from time of diagnosis to clinical staging and finally treatment.

1.0 CHAPTER ONE
INTRODUCTION

1.1 Background of the study

Approximately one out of five breast cancer cases diagnosed in women are known to be HER2-positive status. HER 2 positive disease is a life threatening type of breast cancer which, if not treated, is allied to faster disease progression and leads to poorer chances of survival compared to HER2- disease that is receptor negative. A total of 334,000 women globally are approximated to have breast cancer according to diagnosis ,with breast cancer that is HER 2 positive yearly (Ferlay et al., 2015) that translates to up to 25% of breast cancer cases.

This breast cancer type is characterized by specific receptor (which is a protein) called Human Epidermal Growth Factor Receptor 2 (HER-2) (Iqbal & Iqbal, 2014). HER2 receptor is normally found on healthy cell surface and has a role which is important in the cells natural life cycle. The protein signals the cells to grow and then divide. On the other hand, HER2 in extreme amounts resulting from mutation of the gene may result into uncontrolled growth of the cell and finally leading to cancer development. Cancer cell that is HER 2 positive normally has relatively two million receptor proteins on the cell surface that is almost 100 times more in comparison to normal cell.

(Pegram, Konecny, & Slamon, 2000) (Ross & Fletcher, 1999)

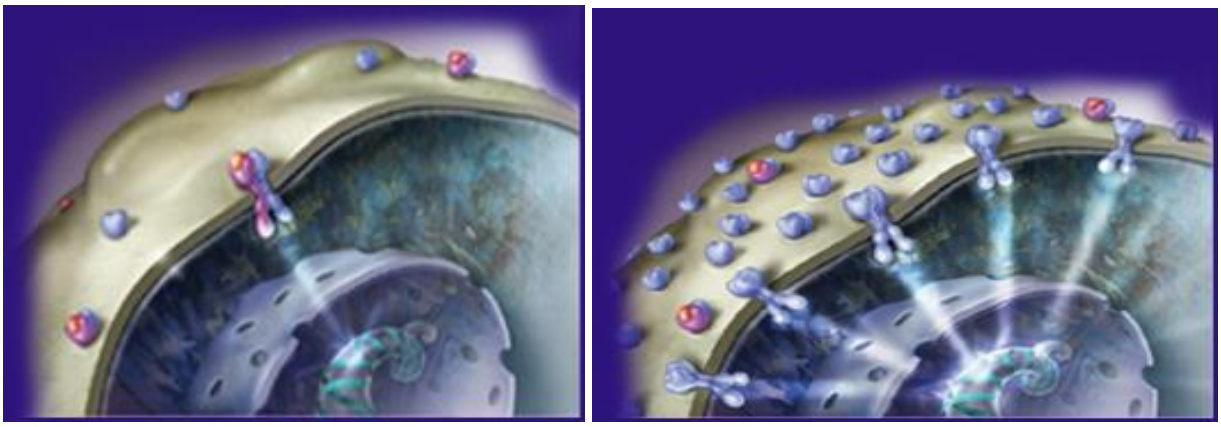


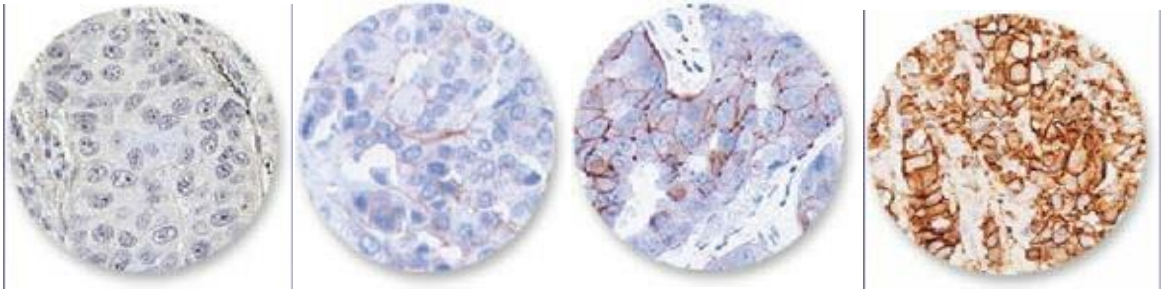
***Figure 1**: The molecular and cellular biology of HER2/neu amplification/overexpression for breast cancer*

Normal (1X) ~ 20,000-50,000 HER2 receptors

Overexpressed HER2 (10X-100X) Up to ~2,000,000 HER2 receptors

HER2 protein expression is analyzed in breast cancer tumour tissue in the laboratory using a technique called Immunohistochemistry. The result is then interpreted and reported by pathologists preferably in specialist centres. The interpretation is performed as stated in the 2013 College of American Pathologists /American Society of Clinical Oncology guidelines
(Fig 2)

***Figure 2**: Semi quantitative scoring of HER 2 using immunohistochemistry on breast cancer tissues* (Vyberg et al., 2015)



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Generally, in 1 out of 5 cases of cancer of the breast, gene mutation occurs in cancer cells which makes too much HER-2 receptor protein hence overexpression/amplification of the HER2 becomes evident in approximately 15 to 25 percent of tumors thus linked to prognosis that is poor ("HER2-positive breast cancer: What is it? - Mayo Clinic," n.d.)

Treatments which particularly target HER2 are so efficient. The treatments are efficient in that breast cancer outcome for HER-2 positive is really nice. ("HER2-positive breast cancer: What is it? - Mayo Clinic," n.d.). The treatments are: Lapatinib (Tykerb),Ado-trastuzumab emtansine (Kadcyla), Trastuzumab (Trastuzumab) and Neratinib (Nerlynx), Pertuzumab (Perjeta) (Timothy J. 2015). Breast cancer that is HER2-positive is highly curable due to presence of these anti HER2-therapies hence treatment of patients is fairly upfront so that we can reduce risk of the patients experiencing stage IV recurrence ("HER2-positive breast cancer: What is it? - Mayo Clinic," n.d.)

Except for endocrine therapy, the best systemic treatments is trastuzumab, a targeted monoclonal antibody against HER2 extracellular domain which shows very high significant effects (Vici et al., 2014). In metastatic setting, admistration of chemotherapy plus trastuzumab increase time to progression together with overall survival (OS)(D. J. Slamon et al., 2001). Several trials that were randomized demonstrated the influence of the adjuvant trastuzumab on the relapse-free survival (RFS) also on Overall Survival in patients with early breast cancer of HER2-positive tumors status. However, there is limited data available on patients who are treated outside the clinical trials particularly in normal routine practice. Recently the issue was looked at by the Group Trastuzumab in Adjuvant Therapy (GHEA) study that went back to medical records of a total 1,002 patients who were treated in normal clinical setting with the adjuvant chemotherapy plus anti HER 2(trastuzumab) in the 42 centers of Italian oncology (Campiglio et al., 2013). Retrospective evaluations carried out showed a number of adverse outcome of patients that have HER-2 positive status in "pre-trastuzumab" era and also advantage of prognostic outcome of trastuzumab administration when even outside the clinical trials (Vici et al., 2014).

This was a single centre, retrospective analysis of the patients who had early breast cancer of HER-2 positive receptor status who received adjuvant chemotherapy alone or combined chemotherapy and trastuzumab at Aga Khan University Hospital, Nairobi (AKUHN) to establish patient's outcomes in terms of 2 years relapse rate (2 year-RR), recurrence free survival, breast cancer specific survival (BCSS) and overall survival (OS) and explore determinants of the clinical outcomes.

1.2 Problem Statement

Up to 25.6% of Kenyan breast cancer patients were diagnosed with HER 2 positive disease (Sayed et al., 2018). All these were eligible for anti HER 2 targeted therapy. However, the cost of HER 2 is beyond the means of most patients the reasons for which include:

- Low uptake of individual medical insurance cover
- Most insurance companies do not include targeted hormone therapy in the cancer cover
- Inadequacy of out of pocket funds

The cost of a complete HER 2 targeted treatment is about $70,000 - $110,000 per year and the standard treatment duration ranges from 6 months to 1 year (Kennedy et al., 2007b)

This study examined the benefits of HER 2 therapy in HER 2 positive early breast cancer patients with regards to survival over time. This information will provide useful information to policy makers on the use of HER 2 targeted therapy in our set up and inform policy on provision and inclusion of HER 2 targeted therapy in national health insurance schemes and private health insurance.

1.3 Objectives

1.3.1 Broad objective

To determine the survival of sub groups of eligible HER2 positive early breast cancer patients receiving combined Trastuzumab and chemotherapy and those receiving chemotherapy only in Aga Khan University Hospital (AKUH), Nairobi.

1.3.2 Specific Objectives

1. To determine association between social (Level of education, employment status, professional background and insurance cover) and demographic characteristics of the patients with HER 2 Neu positive breast cancer.
2. To determine association between survival outcomes and clinical parameters (age) and pathological characteristics (tumour grade) of HER 2 Neu positive breast cancer patients.

1.4 Research Question

1. What is the association between Trastuzumab use and survival among HER 2 Neu positive breast cancer patients?
2. Is there association between social and demographic characteristics of Her 2 positive patients?
3. Is age and tumour grade clinically associated with the survival outcomes of Her 2 positive patients?

2.0 CHAPTER TWO
LITERATURE REVIEW

According to (Ferlay et al., 2015) it was found that cancer of the breast is common and most malignant neoplasm globally indicating approximately 25.2% of cancer new cases among women. Data obtained by Surveillance Epidemiology and End Results Programme(SEER) show that almost 12.5% women from American will at some point of their lives have breast cancer disease("Cancer Statistics Review, 1975-2012 - Previous Version - SEER Cancer Statistics Review," n.d.) (Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, 2014). There has been an increase in the last few decades in amount of the cases diagnosed in the earlier stages. This showed stage I tumours which represent about half the cases of diseases that don't spread currently. SEER observed 15 % increase from 1990 to 1998 in the incidence of T1 tumours (0–2 cm) in UN (United States) (from 143.5–163.5 per 100,000). This then led to noticing of tumours that were non-palpable by spreading of screening programmes plus mammography in that population (Kennedy et al., 2007a).

In about 20% of breast tumours there is overexpression of Human epidermal growth factor-2 (HER-2+) which is related with survival rates that are worse especially with positive lymph nodes population. According to (Vaz-Luis et al., 2014a), only 10–15% of HER-2 positive have sub centimeter tumours (T1ab) that show the increased advancement of the tumours as diagnosed more frequently at stages that are more advanced.

Patients who had cancer of the breast smaller than 1 cm experienced a prognosis that was good globally but until recently there was no information regarding HER-2 status. This patients were excluded in clinical trials with adjuvant therapy and only looked at patients who had HER-2+ tumours of the breast (D. Slamon et al., 2011).

T1ab breast cancer patients with no lymph node involvement have generally good prognosis with ten years breast cancer specific survival greater than 95% (Hanrahan et al., 2007), though not all the studies were systematic in terms of survival rates that were reported. The difference observed was related to those intrinsic heterogeneity and also the limitations of studies that looked at the issue, including: different methodologies, techniques and definitions of HER-2 status, heterogeneity of use of adjuvant systemic treatments and reduced sample sizes (for example,

different metrics for survival used in most studies. Some of the reports showed disease-free survival (DFS) while others recurrence-free survival (RFS) which is similar to DFS, not including primary cancers which are new whether of contralateral or ipsilateral and others preferred breast cancer specific survival (BCSS) or distant DFS (DDFS) (Chia et al., 2008).

According to (Press et al., 1997), among the first studies one of them analyzed prognosis for sub centimeter tumours which had patients totaling to 242 with negative lymph node breast cancer which was reviewed in that population with HER-2+ tumours turning up to be 19% while HER-2 negative (HER-2-) turned to 83%. HER-2 negative and HER-positive tumours had two years RFS of 94% and 83% respectively ($p < 0.05$). HER-2 positive status was the independent variable of prognosis in that study infracentimetric tumours population, with recurrence relative risk of 4.6 (at 95% confidence interval 1.0–20.6) together with relative risk of death of 11.1 (95% confidence interval 1.0–122.8) while comparing HER-2 postive and HER-2 negative tumours .A study was conducted in 2003 by Finnish group (Joensuu H, et al.,2003) which had 852 patients with stage I disease(36.7%) of these T1ab resulting to a relative risk of 2.6 for DDFS for nine years for the HER-2 positive tumours (89% at 95% confidence interval 1.1 $p < 0.01$) in comparison to HER-2 negative tumours (73% at 95% confidence interval 6.2; $p < 0.01$) . Chia *et al* observed 2026 negative lymph node breast cancer patients of which the analysis showed 10.2% were HER-2 positive. The cohort had 10-years RFS lower for the HER-2 positive tumours (65.9% % $p = 0.01$) compared to HER-2 negative tumours (75.5% $p = 0.01$). Though the number of infracentimetric HER-2+ tumours for that cohort was small with sample size of 21 subjects. At the MD Anderson Cancer Centre, in 2009 Gonzalez *et al* published a retrospective study with a total of 965 patients who had T1ab tumours and were treated for 12 years which included patients who didn't receive adjuvant chemotherapy or trastuzumab treatment. It showed HER-2 positive receptor status which strongly related to worse RFS at five years was translating to 77.1% and 93.7% and p. value of 0.001. Additionally the study had 350 tumours from the Institute Jules Bordet and Leoben General Hospital as validation cohort that revealed RFS that was lower at five years for HER-2 positive tumours group that is 87% versus 97% at p. value of 0.043. Curigliano and the collaborators published 2130 T1ab breast cancer patients at the end of the same year and 150 (7%) had HER-2 positive but then looked at the prognostic role of HER-2 status for small tumours (Curigliano et al., 2009). A follow-up after 4.6 years was done which resulted to relative risk of 2.4 at 95% confidence interval 0.9–6.5 p. value of 0.09 and HER-2 overexpression was associated with five

years DFS. According to (Vaz-Luis et al., 2014b) 520 patients who had HER-2 positive disease with T1abN0 tumours and were not administered with adjuvant treatment or trastuzumab which didn't exceed 7%, out of a series of more than 4000 subjects were reported with 5 years distant relapse (Vaz-Luis et al., 2014b). (Fehrenbacher et al., 2014) found that after examining 234 HER2 positive patients with T1ab tumours the prognosis of 171 patients who did not receive chemotherapy/ trastuzumab between 2000 and 2006 was in overall good with 10% recurrence rates (local and distant recurrence free interval) at 5 years in all the sub groups.

There was no clarification on the impact of HER 2 positive hormone receptor in the population. In National Comprehensive Cancer Network (NCCN) series, invasive disease-free survival (IDFS) at 5 years was found in T1b tumours which had 68% as compared to 86% in hormone receptor positive T1b tumours (Vaz-Luis et al., 2014b). The same series found the 5 years DDFS were similar in both groups at 94% for the patients with human receptor Negative T1b tumours and not treated with chemotherapy/trastuzumab as well as patients with human receptor positive tumours. that are unfavourable in HR- patients at five years.

Data obtained from retrospective studies show importance of adjuvant treatment together with trastuzumab in the population. Survival estimates were analyzed in the treatment and control groups with adjuvant and trastuzumab by the NCCN series. Though the design of the study doesn't allow patients being compared in terms of T1a tumours who were treated with chemotherapy and/ or trastuzumab at five years, the IDFS values were 89% to100% and the DDFS values of 100%. For the treated patients the T1b tumours for IDFS was ranging from 90 to 94% and the DDFS was ranging from 94 to 96% when compared to IDFS at five years of 68 to 86% and a DDFS of 94% for the control group.

The Memorial Sloan-Kettering Cancer Centre carried out a single-centre study and observed a three-years DDFS of 97% in a total of 45 patients who were not given trastuzumab and 100% in the other group of 54 patients given with trastuzumab (McArthur et al., 2011).

The Institute Curie (Paris, France) carried out additional retrospective study which included a total of 97 patients with smaller tumours which were less than 1cm or equal to 1 cm between 2002 and 2008 with no involvement of lymph node. High risk profile patients were given Adjuvant trastuzumab based therapy if considered to have a human receptor with high grade or high mitotic index following the institutional criteria. Out of the 97 HER-2+ patients with T1abN0 a total of 41

patients (42%) were given trastuzumab versus 93% who were given chemotherapy. No recurrence was seen in patients treated with anti HER 2 but 9% of patients who were not given adjuvant treatment combined with trastuzumab had recurrence (Rodrigues et al., 2010).

In the ASCO Annual Meeting 2014 presentation, a meta-analysis performed to evaluate the (OS) and DFS by additional trastuzumab for those tumours that are less than or equal to 2cm and were not dependent on the status of the lymph node in the five randomized clinical trials was published between 2004 - 2013. Out 11,200 patients randomized in the five studies 4220 were eligible for tumour size out of which 2588 were selected to receive trastuzumab and 1632 not to receive trastuzumab). The population of study involved mainly T1c tumours with lymph node involvement. The two groups were analyzed by human receptor status. The groups showed a decline of 30% in RR for the group getting trastuzumab. HR positive patient group showed 8 years cumulative recurrence rate that was 7% below the treatment arm (24.3% and 17.3%) and 3.8% lower cumulative mortality rate (11.8% and 7.8% with p. value of 0.005). (O'Sullivan et al., 2015). Efficacy was attained in patients who were given trastuzumab as compared to patients who were not given trastuzumab in the HER2-positive breast cancer and less than 2 cm tumours. This was a meta-analysis of randomized trastuzumab trials. (Peeters et al., 2014).

Worldwide studies have suggested that generally, the tumours have excellent prognosis with no treatment and in most cases recommendable outcomes with no anti-HER-2 therapy might be expected. As anticipated classical factors of prognosis including hormone receptor status together with size have an impact on prognosis which may influence treatment decision. Such patients should have a balance of advantages (benefits) and disadvantages (toxicity) weighed cautiously. Benefit in most of these cases was less than 5% in reduction of distant recurrence risk. Leading to the idea of developing toxic treatments (da Fonseca Reis Silva & Ribeiro, 2015).

Her 2 positive breast cancer remains a significant scientific, clinical and societal challenge. This gap analysis has reviewed and critically assessed enduring issues and new challenges emerging from recent research, and proposes strategies for translating solutions into practice (Ferlay et al., 2015)

3.0 CHAPTER THREE
METHODOLOGY

3.1 Research design

This was a retrospective cohort design which included HER2-positive, consecutive early breast cancer patients treated in adjuvant setting in routine practice in Aga khan University Hospital from 2012 to 2017. Medical records related to demographic, clinical, pathologic, and socio demographic characteristics, adjuvant therapies and outcomes were retrieved. Anonymized data were entered into a database. Two cohorts were analyzed: patients who received adjuvant chemotherapy without trastuzumab, mostly until 2017 (cohort A), and patients who received adjuvant chemotherapy followed by or combined with trastuzumab (cohort B), starting from 2012. Endocrine treatment and radiotherapy were given whenever indicated. Pathology assessment performed on surgical specimens by pathologists of Aga Khan University Hospital were extracted from reports in the Laboratory Information System and all data were collated.

3.2 Study variables

3.2.1 Independent variables

Pathological characteristics

a) Tumour grade

Clinical characteristics

a) Age

Socio demographic characteristics

a) Employment
b) Level of education
c) Insurance

3.2.2 Dependent/Outcome variables

HER 2 Neu positive hormone receptor status

3.3 Study Area and period

The study was conducted at AKUHN, a tertiary cancer care center in Kenya from March 2019 to October 2019.

3.4 Study population

Breast cancer women with HER 2 Neu Positive receptor status who were diagnosed and received adjuvant therapy alone and or adjuvant therapy plus anti Her-2 treatment at AKUHN.
Between January 2012 and December 2017. Estimates showed that a total of 166 women were Her-2 positive in the TNBC study but this study enrolled 83 patients for whom follow up information was available for analysis.

3.4.1 Inclusion Criteria

Eligible patients were histologically confirmed. Completely or partially excised invasive breast cancer with HER2 overexpression or HER2 amplification was assessed in AKUHN. Results on immunohistochemical analysis (IHC) at AKUHN (Herceptest, Dako) of 3+ (IHC 3+), in a range from 0 to 3+ with higher values indicated increased overexpression, were used for confirmation of the status of tumors assessed at the AKUHN as IHC 3+, and a positive result on fluorescence in situ hybridization (FISH) for *HER2* amplification (PathVision, Vysis) at a referral laboratory were required for tumors that were assessed in AKUHN as IHC 2+ or FISH-positive.

3.4.2 Exclusion Criteria

1. All male breast cancer patients
2. All patient with Stage 4 HER2 positive breast cancer

3.5 Sample size

Used an estimated sample size of 83 patients. Since, the population value was small, the strategy was to use the entire dataset. Additionally, the secondary data was available and accessible.

Since was comparing two groups a statistical power of 80% (Romond et al., 2005) was used.

3.6 Sampling procedure

Subjects were recruited based on commencement of cancer treatment at AKUHN.

3.7 Research tools

Previously collected data in Microsoft excel were used to perform analysis.

3.8 Data collection procedures

This involved examining existing data from Triple Negative Breast Cancer (TNBC) data base and oncology records.

3.9 Data Management and Analysis

Cox regression analysis was carried out to evaluate the independence of pathological characteristics, clinical characteristics and socio demographic characteristics in predicting the outcome of HER 2 neu positive early breast cancer patients. The Hazard Ratio and confidence limits (CI) was also estimated for each variable. Significance was defined at the $p \leq 0.05$ level. Definitive analysis was scheduled after determining the primary end-point events (overall survival). Survival curves were plotted using the Kaplan–Meier from the date of diagnosis until the time of death for breast cancer (BCSS), death for any causes (OS), relapse (RFS), or last visit (OS and RFS). Survival curves were truncated at that time-point where the recommendations according to (Pocock, Clayton, & Altman, 2002) were satisfied. The log-rank test was used to assess differences between subgroups. Significance was defined at the $p \leq 0.05$ level.

STATA version 15 was used for statistical evaluations.

Frequencies, percentages, means, median, interquartile range and standard deviations were analyzed for socio-demographic characteristics.

Cox regression model (Oakes, 1981):

$$h(t|x) = h_0(t)e^{\beta_1 x_1 + \cdots + \beta_p x_p},$$

Kaplan Meier(Survival probabilities) (Goel, Khanna, & Kishore, 2010)

$$S_t = \frac{\text{Number of patients treated with adjuvant therapy} - \text{Number of patients treated with neoadjuvant}}{\text{Number of patients treated with adjuvant therapy}}$$

Log Rank test statistic(Goel et al., 2010)

$$\text{Log-rank test statistic} = \frac{(0_1 - E_1)^2}{E_1} + \frac{(0_2 - E_2)^2}{E_2}$$

3.10 Ethical considerations

Ethical approval from AKUHN scientific and ethical committee was sought. The data extracted was stored in a password protected database and confidentiality of participants was maintained as all personal data was identified. The data was kept safe from unauthorized access, accidental loss or destruction and was only accessed by the project supervisors and the student during the study period. Data in hard copies was kept in safe locked cabinet whereas softcopies were kept as encrypted files in the computer during the period of study. The data has been planned to be kept for seven years including up to after publication and award of degree in order to preserve the ability to validate the research findings.

4.0 CHAPTER FOUR
RESULTS AND DISCUSSION

4.1 RESULTS

From 2012 to 2017, we diagnosed 166 patients with HER2-positive early breast cancer disease (Figure 5), out of which 57 received adjuvant therapy alone and 26 received adjuvant plus Her 2 blockade (Table 1) according to adjuvant setting.

We lost follow up to half of the patients who were from other participating institutions and dropped 4 patients who had clinical stage IV breast cancer.

There is sufficient randomized trial based data available to confirm the significant survival benefit of adding trastuzumab to adjuvant therapy in patients with HER 2 Positive disease. However in our data set the overall survival outcomes were not statistically different using Log-rank test (P-value=0.172) (figure 4), this could well be explained by our small sample size and a shorter (2 years) period of survival analysis. In addition a large population of our patients were lost to follow up and therefore were not available for analysis.

4.1.1 Socio-demographic information on treatment groups (table 1)

56.6% of patients are self-employed out of which 63.2% did not receive trastuzumab while 42.3% received the Trastuzumab treatment.

Out of the 22.9% that were formally employed, 21.1% were not able to receive Trastuzumab while 26.9% could afford.

20.5% were unemployed, out of which 15.79% did not receive Trastuzumab and 30.8% received Trastuzumab.

Patients with tumour grade 3 had higher percentage (61.5%) in treatment with trastuzumab compared to grade 1 and grade 2.

Most patients received treatment in adjuvant setting (32(56.1%)) though not all receive anti-HER-2 treatment (24(92.3%).

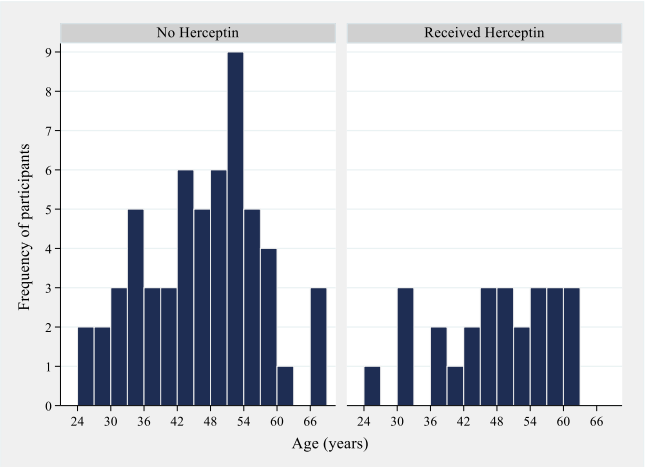
19.2% of participants who received neo adjuvant treatment managed to receive Trastuzumab.

Table 1: Participants' information by treatment group

Variables	Received Trastuzumab		Total n(%)
	No n(%)	Yes n(%)	
Employment Status			
Self-employed/informal	36(63.2)	11(42.3)	47(56.6)
Formally employed	12(21.1)	7(26.9)	19(22.9)
Unemployed	9(15.79)	8(30.8)	17(20.5)
Education level			
Primary	10(19.2)	3(14.3)	13(17.8)
Secondary	24(46.2)	3(14.3)	27(37.0)
Tertiary	18(34.6)	15(71.4)	33(45.2)
Tumor grade			
Grade 1	7(12.3)	3(11.5)	10(12.1)
Grade 2	18(31.6)	7(26.9)	25(30.1)
Grade 3	32(56.1)	16(61.5)	48(57.8)
Adjuvant setting			
No	25(43.9)	2(7.7)	27(32.5)
Yes	32(56.1)	24(92.3)	56(67.5)
Neo-adjuvant setting			
No	43(75.4)	21(80.8)	64(77.1)
Yes	14(24.6)	5(19.2)	19(22.9)

4.1.2 Treatment by age distribution

***Figure 3**: Age distribution of study participants by treatment group*



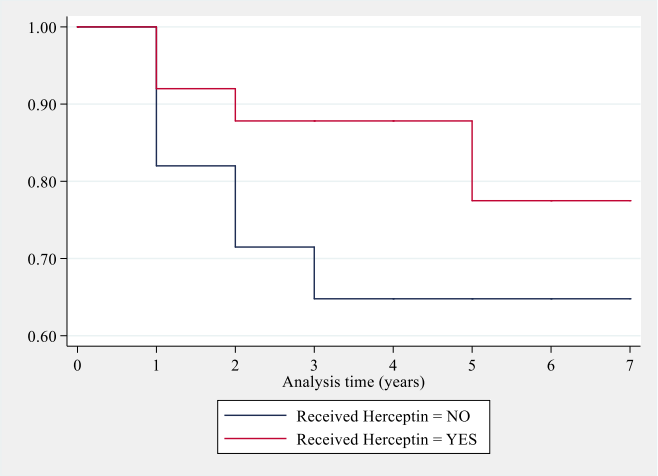
Median (IQR) and minimum, maximum ages by group:

Trastuzumab - 48.5(41-56) min (24) max (62)

No Trastuzumab - 47(37-53) min (25) max (68)

4.1.3 Kaplan Meir curve for comparison on survival experience

***Figure 4**: Comparison of survival experience across study time*



Log-rank test: P-value=0.172

Interpretation: There was no statistically significant difference in the survival experience between the two groups across the study period (95% significance level).

4.1.4 Independent variables in predicting outcome of HER 2 neu positive early breast cancer patients

Table 2: Cox regression analysis results

Covariates		Hazard Ratio	Std. Err.	P-value	(95% Conf. Interval)	
Received Trastuzumab						
	No	1.00 (Ref.)				
	Yes	1.18	0.839	0.821	0.29	4.76
Age (years)		0.98	0.031	0.527	0.92	1.04
Employment status						
	Self-employed/informal	1.00 (Ref.)				
	Formally employed	1.79	1.349	0.443	0.41	7.85
	Unemployed	6.23	4.920	**0.020**	1.33	29.28
Level of Education						
	Primary	1.00 (Ref.)				
	Secondary	1.22	0.741	0.743	0.37	4.01
	Tertiary	0.09	0.072	**0.003**	0.02	0.44
Tumor grade						
	Grade 1	1.00 (Ref.)				
	Grade 2	1.41	0.845	0.566	0.44	4.56
	Grade 3	2.06	1.373	0.276	0.56	7.60
Insurance						
	No	1.00 (Ref.)				
	Yes	0.83	0.515	0.766	0.25	2.80

Controlling for other predictors in the model, those who were unemployed had 6.23 higher hazard of death at any time-point during the study period, compared to those who are self-employed at any given time, given that a patient has survived up to that time-point (CI 1.33-29.28; P.value-0.020). This means that at any given time-point, 6.23 times as many patients who are unemployed die compared to those who are self-employed.

Holding other predictors constant, patients who have tertiary level of education have 91% rate of disease free survival at any time point during the study period as compared to the primary level of education (CI 0.02-0.04, P-0.03).

4.2 DISCUSSION

The evolving field of HER-2-targeted therapy has significantly improved the outcome of early breast cancer in women diagnosed with HER-2-positive receptor status. The treatment with Anti Her 2 based therapies, however, is financial taxing, as being expensive and less accessible. In this study, we sought to find out the ability of women from this part of the world to understand and afford this additional expensive treatment on top of the standard chemotherapy in relation to their demographical characteristics such as educational level, insurance, employment status and age. We also sought to analyze the importance and impact in terms of overall survival of anti Her-2 treatment in adjuvant treatment in a tertiary setting with emphasis on pathological characteristics.

The Log-rank test showed no statistically significant difference in the survival experience between the group that acquired adjuvant therapy alone and that which received both adjuvant therapy and anti HER-2 blockade across the study period (P-value=0.172) at 95% significance level (figure 4).

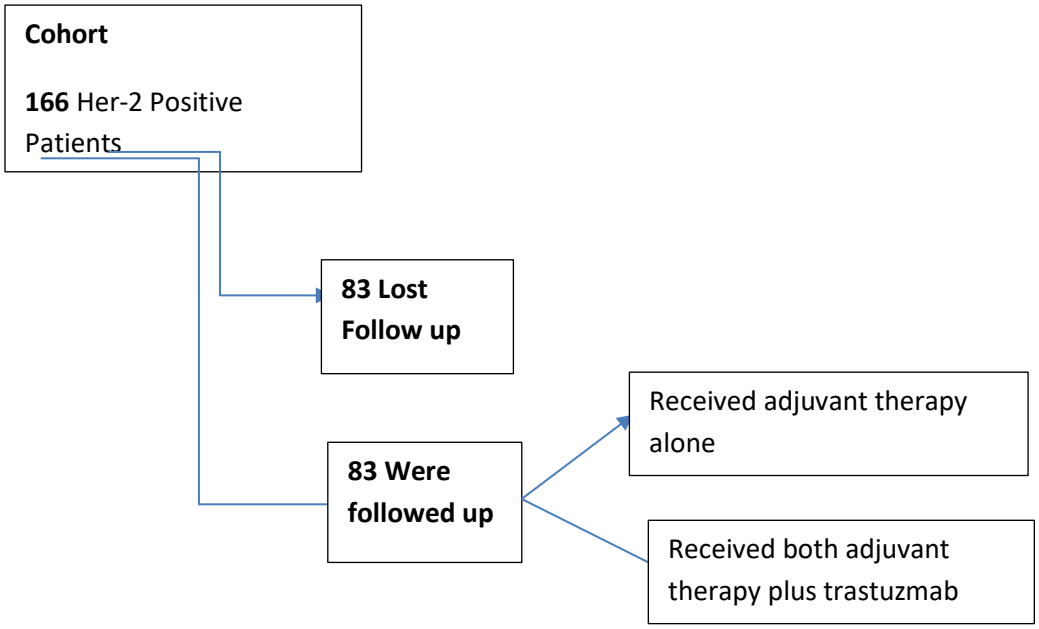
On follow up, those who were unemployed had 6.23 higher hazard of death compared to those who were self-employed at any given time, given that a patient has survived up to that time-point (Table 2).

Participants with tertiary level of education had 91% rate of disease free survival at time point during the study period as compared to the primary level of education (Table 2). This clearly indicated that education played a big role in the management and treatment of HER 2 positive breast cancer disease.

Some patients during the follow up period had no knowledge of anti HER2 blockade therapy answering the question to why they did not receive the treatment.

This was due to loss of patient follow up in the different participating institutions resulting in decrease in sample size.

Figure 5: Diagrammatic representation of follow up data



4.3 LIMITATIONS

1. The sample size was small
2. Loss of follow up data

5.0 CONCLUSIONS AND RECOMMENDATIONS

5.1 CONCLUSIONS

These results suggest knowledge and employment play a big role in cancer treatment especially Trastuzumab treatment leading to prolonged life time in Her-2 positive early breast cancer patients. Also financial status and medical insurance of a patient has an impact on cancer treatment particularly for receiving anti her 2 neu- therapy.

5.2 RECOMMENDATIOS

The government should subsidize the cost of cancer treatment especially to those who are unemployed.

Procedures for cancer treatment should be standardized across all hospitals in Kenya from time of diagnosis to clinical staging and finally treatment.

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