PREVALENCE AND FACTORS ASSOCIATED WITH UPPER EXTREMITY LYMPHEDEMA IN PATIENTS POST BREAST CANCER SURGERY AT KENYATTA NATIONAL HOSPITAL

UNIVERSITY OF NAIROBI

A dissertation submitted as part fulfilment for the award of Master of Medicine in General Surgery at the University of Nairobi

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DECLARATION

I, the undersigned, declare that this dissertation is purely my own original work and has not been presented for a degree in any other university. Wherever I have used another person's work, I have accordingly acknowledged and referenced.

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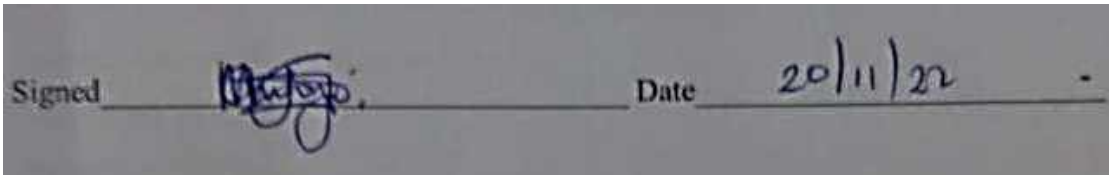

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DEDICATION

To my mum, Margaret; my wife Leah and my children Dave and Amor.

CERTIFICATE OF AUTHENTICITY

This is to certify that this dissertation is the original work of Dr Joseph Mulongo Owuor, M.Med General Surgery student in the Department of surgery, Faculty of Health Sciences, University of Nairobi, under the guidance and supervision of Dr Daniel Oyaka and Dr Marilyn Omondi. This is to confirm that this dissertation has not been presented in the University of Nairobi or anywhere else for the award of any other degree.

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LIST OF ABBREVIATIONS

BCAL - Breast Cancer Associated Lymphedema

CDC - Centers for Disease Control

MRM - Modified Radical Mastectomy

ERC - Ethics and Research Committee

CDT - Combined/Complete Decongestive Therapy

MLD - Manual Lymph Drainage

KNH - Kenyatta National Hospital

QOL - Quality of life

MDTM - Multi-Disciplinary Team Meeting

BMI - Body Mass Index

SPSS - Statistical Package For Social Sciences

ALND - Axillary Lymph Node Dissection

SLNB - Sentinel Lymph Node Biopsy

DCIS - Ductal Carcinoma In Situ

ABSTRACT

Background

Worldwide, Upper extremity lymphedema is among the prevalent debilitating complications post breast surgery. Its impacts are challenging to healthcare systems, healthcare providers, and patients. The incidence of lymphedema varies globally, ranging from 5%-60%. The risk factors to developing lymphedema post breast surgery have also been studied. There has been no study to get the real prevalence and hence the burden of lymphedema after breast surgery in our set up.

Objective

To find out the prevalence of upper extremity lymphedema post breast surgery; and characterize the risk factors associated with it.

Methods and Materials

This was be a 5-year retrospective cross sectional study at KNH records department. Data was extracted from complete medical records of a sample of all breast cancer patients who had undergone an operation for the disease at KNH between January 2014 and December 2019.

A structured closed-ended questionnaire was employed to collect data from the patients' files. The initial data collected was to check the presence or absence of post breast surgery upper extremity lymphedema. This was used to calculate the prevalence.

The data collected at this stage included, the demographics; the diagnosis; radiotherapy post mastectomy; axillary lymph node dissection, sentinel lymph node dissection, adjuvant chemotherapy, neoadjuvant chemotherapy, number of lymph nodes dissected, axillary recurrence, tumor location in terms of quadrants.

This was then entered into SPSS version 24 for analysis. General descriptive statistics were applied to derive frequencies, means, and standard deviations. Data was analyzed continuously and presentation done using means and standard deviations. Categorical data analysis and presentation was done using frequencies and proportions. Statistical significance was then taken at p-value of <0.05 and data displayed in tables, graphs and charts.

Results

A total of 364 participants were included in the study. Mean age of respondents was 50.5±13.8 years and ranged from 12years to 96years. The majority of the participants were between 41-50 years. The incidence of lymphedema in patients who had undergone surgery for breast cancer in our set up was 7.1%.

Among the non-treatment related factors that we studied were; Age, pathology of breast ca (invasive/DCIS), axillary recurrence, BMI, tumor location in quadrants.

There was no significant difference in mean age of participants who developed lymphedema (51.7yrs±16.2) compared to those who didn't (50.4±13.7yrs) (p=0.431). The relationship between diagnosis and lymphedema development was also not statistically significant (with a likelihood ratio of 0.08 and a p=0.928). The same applied to the tumor location/diseased part (p=0.795). The BMI of patients studied ranged from 17kg/m^2 to 35 kg/m^2. With a likelihood ratio of 18.6, and a chi square of 25.3. This was found to be statistically significant (p=0.021). On the other hand axillary recurrence was also found as an independent risk factor (p=0.02).
The treatment related risk factors that we studied included, type of surgery to the breast and to the axilla, adjuvant and neoadjuvant radiotherapy and chemotherapy.
All the patients who developed lymphedema (26 patients) had undergone ALND while none developed after WLE, though this was not statistically significant (p=1).
In our study the use of chemotherapy, whether in the adjuvant or neoadjuvant set up was not statistically significant (p=0.06). This was similar to the relationship between adjuvant radiotherapy and lymphedema which was also not statistically significant (p=0.06)

Conclusions

Our results suggest that the most important treatment and patient-related risk factors for breast cancer-related lymphedema were BMI and axillary recurrence. Clinically it was also noted that all patients who had developed lymphedema had undergone ALND, as opposed to none who had SLNB. Elimination or prevention of these risk factors may reduce the incidence of lymphedema.

CHAPTER ONE: INTRODUCTION

Secondary lymphedema in the upper limb following intervention for breast cancer is a common problem whose incidence ranges from 5% to 60% (1)(2)(3)(4). This variation depends on diagnostic criteria, the modality of treatment and duration of the study(5). A study done by Norman et al, and published in 2009, that was carried over 5 years on more than 600 patients, 5-year incidence was 42% with 89% appearing in the first 3 years (6). The risk decline with time from treatment but it remains a lifelong risk for breast cancer survivors (7).

Upper limb swelling present heaviness and discomfort feelings, disfigurement, functional limitation, distress psychologically, and increased recurrent infection risks (8)(9), affecting quality of life (10)(11)(12) and is one of the complication that is difficult to manage(8).Its effects are long term and are considered major complication(8).

Several studies looking at risk factors have indicated that the number of involved lymph nodes, the number of excised axillary lymph node, radiotherapy, and obesity, weight gain after treatment may influence occurrence of lymphedema (13)(14)(15). However, factors influencing the volume are incompletely known. Some researchers suggested mastectomy has higher volume than lumpectomy and the body weight may also affect it. Management of lymphedema will depend on severity but should begin immediately if the associated factors are known.

While the above figures indicate studies done in the west and in east, we do not know our prevalence and factors influencing the occurrence of lymphedema. In this study, the aim is to establish the prevalence and factors that are associated with upper limb lymphedema in female patients previously under treatment for breast cancer in our set up.

CHAPTER TWO: LITERATURE REVIEW

The condition where protein-rich fluid accumulates in tissues is termed as Lymphedema. Its occurrence is as a result of interruption in the drainage of the lymphatic system by the impaired function of lymph vessels, which is part of the circulatory system.(16).

When there is excess fluid from tissues, one function of lymph vessels is remove it and transport it back to the circulation. This happens through lymph capillaries which are woven like a cobweb in the dermis, then through the subcutaneous lymphatic vessels and later to the thoracic duct and the deeper system. Disruption of this normal flow would cause this fluid to accumulate in the tissues resulting in Lymphedema.

Moreover, the lymphatic system aids in maturation of immune cells which constitutes a critical body defense mechanism.(16).

Worldwide, the most common cancer in women is breast cancer.(17)(18). Survival rates vary, but there is increased survival due to better screening programs and methods, early diagnosis and breakthroughs in treatment.(17)

Upper extremity lymphedema is commonly caused by breast cancer and treatments associated with it(19). The main modalities of treatment for breast cancer are surgery, endocrine (hormone) therapy (ET), radiation therapy (RT), chemotherapy (CT), and targeted therapy.(17)

The initial treatment for majority of early-stage breast cancer patients will be surgery. Although, some early-stage breast cancer patients (patients with triple-negative disease or HER2-positive) and those with breast cancer that is locally advanced may first get treatment using neoadjuvant therapy before surgery.

With surgery, comes attendant complications', including wound infection, seroma formation, hematoma, chronic pain, venous thrombo embolism, upper extremity morbidity, incisional dog ears, breast fibrosis and breast edema (20).

After breast surgery, upper extremity morbidity is common. These include swelling/lymphedema, stiffness, numbness, and pain in the arm and also shoulder stiffness and pain, or nerve injury(19)(21)(22)(23)(24). The impact of this is poor quality of life due to participation restriction and associated long term activity limitations.(22)

Furthermore, a swollen or disfigured extremity is a breast cancer reminder that is always present. It contributes to anxiety, emotional distress and depression in women who are affected.(19) Considering the breast cancer incidence that is increasing worldwide and locally, it is of public health importance to understand the incidence of subsequent secondary lymphedema and risk factors associated with it.

2.1: Normal Lymphatic Anatomy and Physiology

Lymph from interstitial space in various organs is transported by the lymphatic system towards the base of the neck. Tissue fluid from the interstitium is considered lymph fluid when it enters the lymphatic system (25). The lymphatic system pathway starts in tissues after resorption from initial lymph transport and lymphatics to progressively larger vessels; lymphatic trunks and collectors. This finally reaches the confluence of the internal jugular and subclavian veins as lymphatic duct at the right venous angle, and thoracic ducts at the left venous angle (Figure 1 and 2).(26)(27)

The body can be divided into four quadrants with all drained by the thoracic duct except the upper right quadrant according to the lymphatic drainage.(26)

There are two systems of lymphatic drainage that are separate topographically; the superficial and deep system. The skin and subcutaneous tissues are drained by the superficial system, and the tissues deep to the fascia is drained by the deep system. The perforating vessels that traverse the fascia are connected by the two vessels.(27)

This same pattern is replicated in the upper extremities. The superficial upper limb lymphatic vessels initially arise from the lymphatic plexuses in the skin and travel up with major superficial veins. The vessels accompanying the basilic vein drain in the cubital lymph nodes, while those accompanying the cephalic veins drain into the apical axillary nodes. The deep lymphatic vessels accompany the major deep vein draining into the axillary nodes.(28)

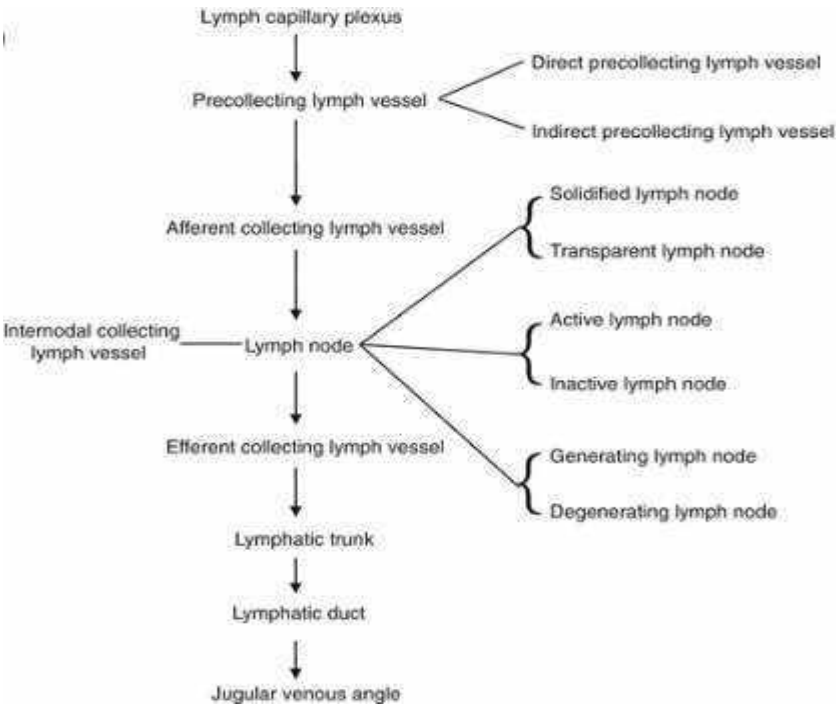


Figure 1. lymph fluid return pathway

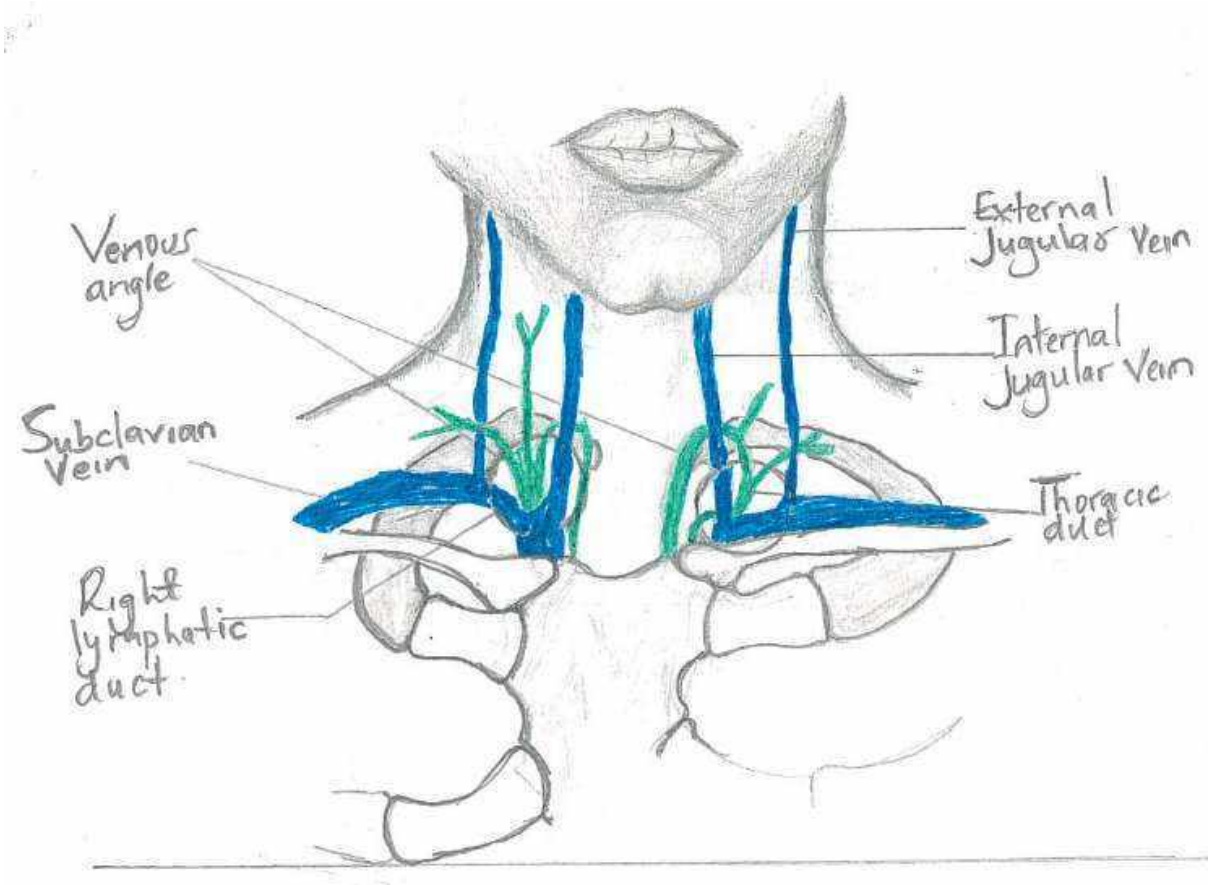


Figure 2; Lymphatics at the venous angle

The lymphatics of the breast follow the same pattern as above. Under the areola lymphatic channels collect to form Sappey's plexus.(29)(30). Three main routes that are parallel venous tributaries from this plexus facilitate the lymphatic drainage; the axillary (75%), the internal mammary (20%), and the retro mammary (5%) pathways. When usual channels are blocked in disease other pathways occur. Through the rectus sheath or through the diaphragm, lymph passes to the contra lateral breast, cervical nodes, peritoneal cavity and liver

The axillary lymph nodes drain the breast tissue about 75% of the time. They are divided into three levels depending on their relationship with the pectoralis minor muscle. Level one lymph nodes are lateral, level two lymph nodes are posterior, and level three lymph nodes are medial to the pectoralis minor (figure 3).(29)

These axillary lymph nodes are further grouped into; an anterior or pectoral group, posterior or sub scapular group, a lateral group, an apical group at the apex of the axilla, receives lymphatics from all the groups named above. The anterior group receives lymphatics from the upper half of the trunk anteriorly and from the major part of the breast while lateral group receive from the upper limb.

With the breast and the upper extremity lymphatics both draining into the axilla, there is considerable overlap and connection. As noted by Pavlista et al, there is a close association between the upper extremity's lymphatic drainage and the breast especially at the caudal part of the axilla.(31)

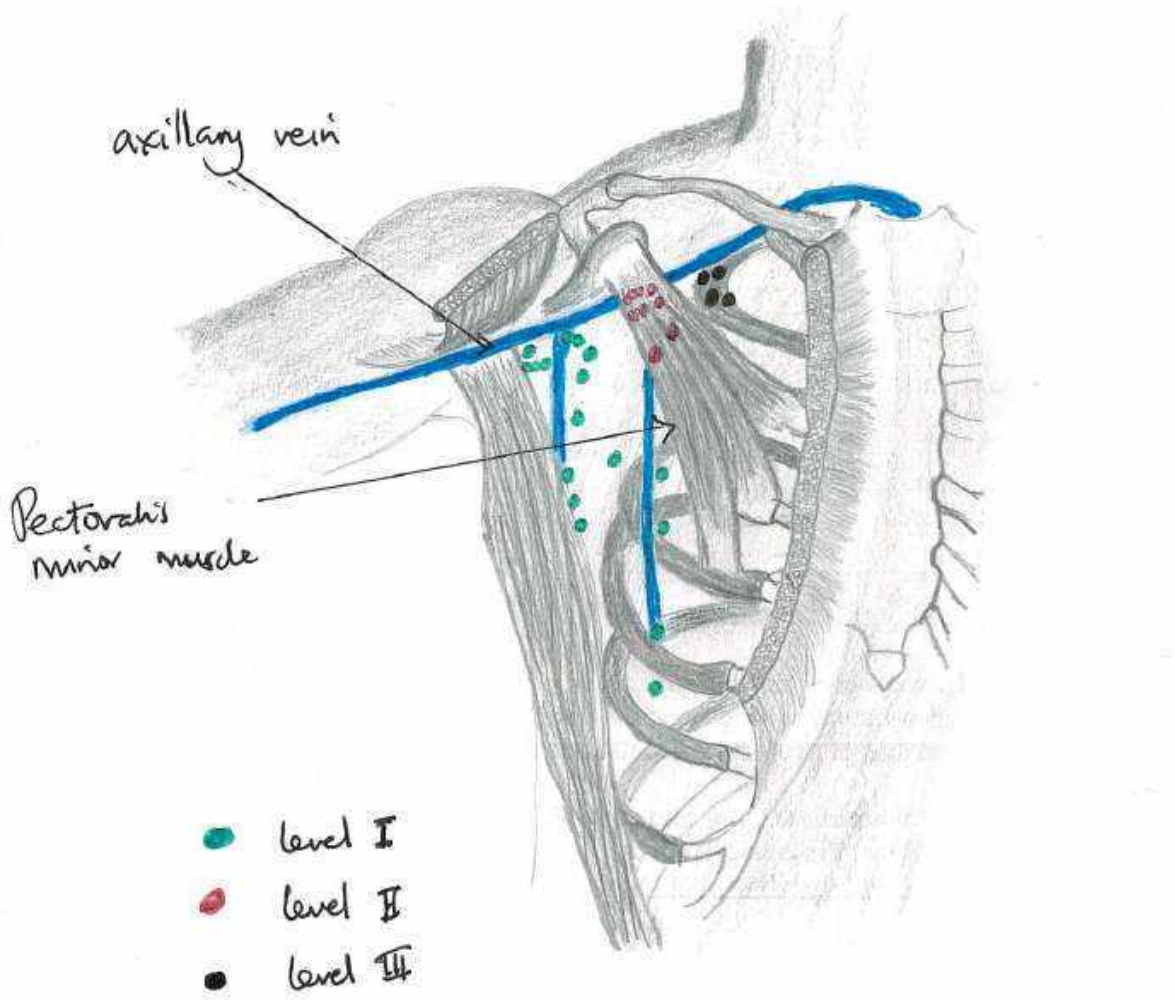


Figure 3. Levels of breast lymph node drainage

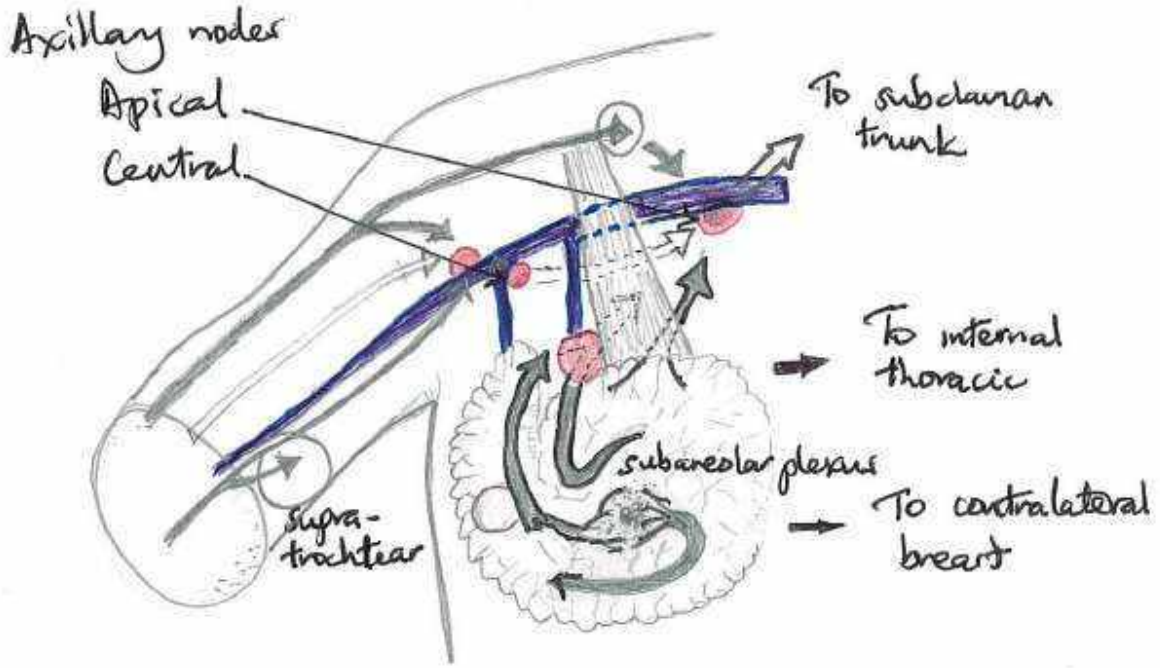


Figure 4: relationship between upper extremity and breast lymphatic drainage

2.2: Pathophysiology of Lymphedema

The lymphatic system absorbs and transports lymph fluid back into the venous system when the physiologic state is normal. The lymphatic load and transport capacity determine its efficiency (25)(32)(33)

The lymph fluid volume, containing cell, fat loads, lymphatic protein water, and hyaluronan is termed as the lymphatic load.(25) The maximum amount of lymph volume that the lymphatics can transport in a given period of time is transport capacity. The lymphatic system is overwhelmed when the maximum transport capacity is exceeded by increases in the lymphatic load, causing lymphatic failure or insufficiency, leading to interstitial edema i.e. lymphedema.(25)(33)

There are three types of insufficiency; dynamic, mechanical and mixed/combined insufficiency. Dynamic insufficiency or high-volume insufficiency occurs when the transport capacity is less than the lymphatic load.

Functional or organic e.g. surgery, radiation, trauma, inflammation causes a reduction in the lymphatic systems transport capacity hence low volume insufficiency or mechanical insufficiency. Breast cancer associated lymphedema falls under this category.

Development of combined insufficiency happens when both mechanical and dynamic insufficiencies are simultaneous. Hence there is a reduction in the transport capacity and an increment in the lymphatic load(27)

Syaza et al proposed that a chain of progressive and complex events are involved in the development of lymphedema that affects various compartments of the tissue.(33) These include:

i. Remodeling and expansion of the adipose tissue. Existing substantial evidence suggests lymphedema tissue swelling is not only due to accumulation of fluid, but also due to fat deposition. There is proper documentation of the presence of excess adipose tissue in the affected limb following breast cancer in patients with chronic non pitting arm lymphedema.(34). This fat deposition is in the epifascial compartment and the subfascial compartment(35)
ii. The deposition of excess extracellular matrix in the lymphatics, fibrosis, potentially causes their dysfunction. Experiment has revealed an increase in the amounts of collagen fibers in the edematous skin (36)
iii. In the later stages lymphedema as it progresses, changes in the skin like hyperkeratosis may occur together with fibrosis of subcutaneous tissue, dermis, and muscular fascia. Later, the skin becomes indurated developing a leathery texture and is more prone to recurrent infections, cellulitis, wart formation, and ulceration.(37)
iv. Lymph stasis that occurs as a result of lymphatic obstruction or insufficiency.(32)(33)(16). Experiments have shown that lymphatic stasis and leakage can promote adipogenesis and adipose tissue hypertrophy. Harvey et al, showed that fat accumulates near leaky lymphatics and this fluid induces differentiation of adipocytes (38)
v. Inflammation- studies have shown that there is infiltration of inflammatory cells in the edematous tissues in lymphedema. The majority of these cells are CD4+ T cells and they contribute to the pathological changes including fibrosis.(39)(40)

2.3: Causes of Lymphedema

The two general classifications of lymphedema are secondary and primary.

Primary lymphedema development begins when genetic abnormalities occur affecting the lymphatic function/ or development. This is usually congenital or hereditary. (16)(32)(27)(41) These various conditions include; Hypoplasia which is due to reduction in the numbers of lymphatic collectors and the decreased diameter of existing lymph vessels; Hyperplasia due to

increased diameter of lymphatic collectors; Aplasia due to absence of components of the lymphatic system; and Inguinal lymph node fibrosis.

Mechanical insufficiency causes secondary lymphedema; this can be due to tumoral blockage, infection, trauma, surgery, radiation, and immobility, chronic venous insufficiency, or tourniquet effects. In the USA, the most common cause of secondary lymphedema is a consequence of the treatment of breast cancer, especially when axillary surgery is combined with radiation.(27)

The causes of lymphedema are summarized in the figure below

Lymph Drainage Failure

	Mechanism		
Reduced lymph-conducting pathways	**Hypertrophy or hyperplasia of lymphatic vessels**	**Functional failure**	**Obstructed lymphatics**
Possible causes			
Aplasia or hypoplasia of whole vessel	Lymphangiomatosis, lymphatic malformations	Valvular failure	Lymph node abnormalities (e.g., fibrosis)
Acquired obliteration of lymphatic lumen (e.g., lymphangiothrombosis, lymphangitis)	Megalymphatics	Disordered contractility	"Scarring" from lymphadenectomy, radiotherapy, or infection

` **Figure 5: causes of lymphedema**

2.4: Risk factors associated with the developing upper extremity lymphedema post breast surgery

The likelihood of a person to develop lymphedema is mainly dependent on the individual risk factors of the patient. Generally, these potential risk factors are classified into nontreatment-related or treatment-related. There are other non-modifiable risk factors that are less researched and not well-understood they include genetics and anatomy.(42)

The treatment related risk factors are;

I. Type of axillary surgery. The type of surgery done on the axilla largely establishes the risk of an individual for developing lymphedema. The patients is put at life-long risk for developing lymphedema by SLNB and ALNB due to the removal of either few sentinel lymph nodes, in the case of SLNB or many axillary, in the case of ALND.(42). Recent data estimated that patients' incidence with unilateral breast cancer who receive ALND is four times more than those who receive SLNB. This suggests that while minimizing the risk of lymphedema in patients with early breast cancer or clinically node negative breast cancer SLNB is an effective option for staging the axilla. (9)(42)

The number of nodes removed has also been implicated as a risk factor to development of lymphedema. Kim et al showed that BCRL incidence rates in patients with 10 or

more axillary lymph nodes removed were significantly greater than in patients with less than 10 dissected lymph nodes i.e. 27% vs. 6% respectively. (43) Hayes et al demonstrated that having more than 20 lymph nodes removed during axillary dissection (irrespective of extent of surgery) increases odds of developing lymphedema four-fold(9).

II. Radiotherapy to the regional lymph nodes. Postoperative radiation therapy is an additive risk factor to axillary node dissection and it also increases the risk for lymphedema. Kissin and colleagues found that the incidences of subjective lymphedema with axillary node dissection alone and axillary node dissection plus radiation therapy were 7 and 38 percent, respectively(44). Even without ALND, patients who receive regional lymph node radiotherapy should be considered a high-risk group for developing lymphedema, and all patients undergoing ALND and/or regional lymph node radiotherapy should be prospectively screened.(42)

III. Adjuvant and neoadjuvant chemotherapy. This has not been well documented as some studies suggest it is a potential risk factor, while others do not. Especially taxane-based chemotherapy because of taxane-induced fluid retention in patients during treatment. Kilbreath et al in a prospective cohort study found that arm swelling at 6 and 12 months was associated with adjuvant taxane therapy(45)

The effect of neoadjuvant chemotherapy on BCRL risk is still unclear though it has been suggested that neoadjuvant chemotherapy could decrease BCRL incidence by reducing the number of positive lymph nodes(46)

The risk factors that are non-treatment related include;

I. Age. The age at which breast surgery is done has been shown to impact development of lymphedema. Although some researchers show no association, others have proven that younger age is a risk for BCRL development. Armer et al found that women aged younger than 60 years had were more likely to get lymphedema (41.2% versus 30.6%) in comparison with aged more 60 years and above.(4)

II. Pathology of breast cancer. It has been shown that the risk of lymphedema is more in invasive carcinoma than in non-invasive carcinoma. Ziping et al found that lymphedema incidence was far higher among patients at the stages T1, T2, and T3 compared with those at stage Tis. Though the incidence did not significantly differ among the T stages. It was also unrelated to the diseased part of the breast.

Lymphedema incidence was 4.7% for DCIS, and 11.3% for infiltrating ductal carcinoma. (47)

III. BMI. High BMI is a risk factor that is well-established at the time of diagnosing breast cancer for developing BCRL. Jammallo et al found that the independent risk factor for

BCRL was a BMI was an when equal to or greater than 30 kg/m2 (48). Another risk factor for BCRL as suggested by some supporting evidence may be weight fluctuations during and after treatment.

Werner et al found that BMI was the variable closely associated with arm edema development. (13). They found that obese women had a 5-year arm edema incidence that was beyond double that of the non-obese i.e. 27.4% vs 12.5%.

IV. Cellulitis. It is also a risk factor that is well-established for BCRL. Ferguson et al demonstrated that cellulitis and infections significantly increased the risk for BCRL. (49). The converse is also true, with BCRL increasing the risk for infections.(50)

V. Other possible non treatment related factors include level of education, the arm affected whether dorminant or non dorminant, and presence of a supportive partner

2.5: Stages and Severity of Lymphedema

During the early stages, the accumulation of lymph fluid in the interstitium is often not clinically evident, but occurs if the transport capacity of the lymphatic system becomes more than the lymphatic load. As such, lymphedema is classified into 4 stages, from the latency stage which shows no clinical signs, to stage 3 which is the worst form.(27)(51)

Stage 0, (Latency stage). The patient does not present with outward signs of edema but is considered "at-risk" for lymphedema development due to injured lymphatic vessels. This includes patients with breast cancer who have undergone radiation and or sentinel lymph node biopsy but there is no development of a swelling. There is a reduction in lymphatic transport capacity, predisposing the patient to lymphatic overload and resultant edema. A feeling of heaviness may be reported by the patient.

Stage 1 (Spontaneous). This is reversible. It is characterized by pitting edema with no fibrosis. At this stage the swelling is soft; it may respond to elevation when prolonged

Stage 2 (Spontaneously irreversible). This has tissue fibrosis/indurations. There is no response to elevation on the swelling. As the limb volume increases, skin and tissue thickening occur. There may be the presence of pitting but difficulty in assessment due to skin and or tissue fibrosis

Stage 3 (Lymphostatic elephantiasis). This stage is characterized by pitting edema, fibrosis and skin changes. Papilloma may form during this stage, infections/cellulitis may occur, and the skin becomes dry.

From the above it is clearly evident that early detection and treatment of lymphedema (before the condition becomes irreversible) is of the utmost importance(27)

2.6: Signs, Symptoms, Diagnosis, and Evaluation

The symptoms include; limb aching or discomfort, a heaviness or tightness feeling in the limb, swelling in a portion or entire limb, and restricted range of motion of the limb.(27)

In the adjacent upper quadrant of the trunk swelling may be present. There is usually little or no pain, while the skin color is generally normal, though in advanced lymphedema, there may be hardening and thickening of the skin. The swelling is usually unilateral and with a Stemmer sign presented by the patient (especially on the lower limb)

Development of lymphedema risks are life-long. It may be delayed for a long time (several decades) or occur at the onset of the initiation of treatment (52)(53). Patients presenting new onset swelling after undergoing surgery or radiation therapy must undergo thorough workup. Performance of a thorough examination and history is necessary to establish the cause, either a recurrence or metastasis that may be blocking the lymphatics. For further evaluation and management once this is done, the patient should be referred to physiotherapy.(16)(27)

In evaluating for lymphedema, the following should be performed(16)(27)(51);

Skin inspection and palpation, check for the presence or absence of fibrosis, tissue consistency, skin mobility, and edema whether pitting or non pitting.

Performing measurements of girth and volume and photography should be done. A 2.0 cm girth difference, a 10% increase in volume or a volume difference of 200 mL between the two limbs (the uninvolved versus involved limb) should be indicative of lymphedema.(27)(51)(4). At matched anatomical location along the arm, girth measurement should be done. The difference could be between the same location (including side) at different visits or could be either between sides within a visit, having established a baseline. Different methods can be used for volume measurements: infrared optoelectronic assessment, calculation of estimated volume, bioimpedance, and water displacement.(27)(51)

Once a patient is diagnosed with lymphedema, treatment should commence immediately.

2.7: Management of Lymphedema

There is no cure for secondary lymphedema. Emphasis should therefore be placed on prevention and risk reduction. The goal should be to avoid lymphedema entirely, and if it occurs then to reduce it or prevent worsening. (16)(53)

Among these strategies for prevention and risk reduction include; Educating patient who are at risk about prevention and treatment. For a success before the start of any treatment, the patient must thoroughly understand and have firm commitment to all treatment components and maintenance program. Avoiding limb constrictions and infections that may trigger cellulitis and lymphedema is also important. Other strategies include minimizing treatment related trauma to the nodes in the axilla; and behavioral and hygiene strategies e.g. weight loss for obese patients

When lymphedema has established itself, the interventions are categorized into

- Conservative or nonsurgical therapy. Most of lymphedema patients are managed non-operatively
- Surgical therapy is usually the patient's secondary option for those who had failed initial conservative measures, or those that plateau at a level unsatisfactory to the patient despite strict adherence to compression and manual lymphatic drainage regimens.(51)(54)

Conservative management: this consists of combined decongestive therapy and exercise or complex decongestive therapy (CDT). 4 components are in CDT, compression therapy; remedial arm and shoulder exercises; manual lymphatic drainage (MLD); and deep-breathing exercises to enhance venous and lymphatic flow.(55)(56).

Surgical therapy: these are usually classified into 2; ablative therapy and physiological therapy.(51)(57).

In ablative surgery, the edematous and fibrotic soft tissues, above the level of the deep fascia, are removed surgically. This is done with either liposuction or direct excision. Examples include, the Charles procedure, in which all the lymphedematous skin above the deep fascia is excised and split thickness skin graft is used to cover the remaining wound. (51). There is also the suction assisted lipectomy/liposuction.(35)(51)

The flow of lymph fluid out of the affected limb is recreated by normal or alternate routes using physiologic methods. Currently, two main physiologic interventions are in practice for the treatment of lymphedema. The first is based on the principle of creation of shunts between the congested lymphatic channels and the venous system proximal to the site of lymphatic obstruction. The second relies on grafting vascularized soft tissue flaps which usually include vascularized lymph nodes to the affected extremity.(51)(58). These include; lymphaticolymphatic bypass, lymphaticovenular anastomosis, vascularized lymph node

transfer, vascularized omental flap transfer, and simultaneous microsurgery breast reconstruction with vascularized lymph node transfer.(51)(57)(58)

2.8: Upper Extremity Lymphedema and Morbidity Experience in the World

The effects of breast cancer-related lymphedema are detrimental and present challenges to healthcare systems, healthcare providers, and patients. Afflicted patients are predisposed to physical disability and disseminated infection is common among afflicted patients. Moreover, management regimes are often demanding with frequent office visits, and burdensome compression garments including conservative physiotherapy, all of which have impacted the quality of life negatively.(59)(60). These frequent visits especially due to complicated lymphedema exert a substantial burden to health systems due to disproportionate resource utilization.

The burden of upper extremity lymphedema post treatment of breast cancer, and its associated factors is therefore an entity of public health concern world over.

In the United States, Stout et al compared the direct costs of a traditional model of care and a prospective surveillance model, in breast cancer related lymphedema.(61) They found that the traditional model of care (in which patients are referred only if/when they developed lymphedema) was more costly compared to a new method of prospective surveillance (where all patients are seen as a baseline, then followed up prospectively and lymphedema identified and treated early). The cost of treatment was five times more in the traditional group. They concluded that a paradigm shift should be encouraged where physiotherapists are brought in early to start prospective surveillance.

Chrischilles et al looked at upper extremity disability and quality of life after breast cancer treatment(22). They looked at a combination of surgery and radiation. Complications from these treatments included fibrosis, cording, neuropathy and lymphedema, all of which impacted negatively on the quality of life. They also demonstrated that early physiotherapy intervention, such as manual therapy, early mobility, range of motion exercises, lymphedema education, and/or scar management, and have demonstrated a lower incidence in arm and shoulder morbidity and better QoL in patients following breast cancer surgery.

In a meta-analysis by Petrek et al, they reviewed publications on breast cancer related lymphedema from 1970 to 1998. They found that that lymphedema incidence ranged from 6% to 30%. Additionally, they found that the definition of lymphedema, measurement techniques, length of follow-up, source of patients, varied from report to report. They concluded that there has not been a definitive study to date performed to establish lymphedema incidence and that there hasn't been any prospective study where patients have been followed at intervals with accurate measurement techniques over the long term .(62)

In Europe, Kootstra et al, in the Netherlands compared the upper arm morbidity in early breast cancer, treated with axillary lymph node dissection versus those treated with sentinel lymph node biopsy. They found that arm volume increased more with ALND compared with SLNB. They also found that in patients with ALND, the arm volume continued to increase even 2 years post-surgery, while for those with SLNB, the volume increased then stabilized.(21)

Vignes et al, in France studied the factors related to an increased volume of lymphedema related to breast cancer.(63). These included; a high BMI, past history of cellulitis and a longer duration of edema. They concluded that the controlled parameters to prevent severity of breast cancer-related lymphedema in women are mainly weight control, diagnosis and management of lymphedema at early stages, and advices to avoid cellulitis.

In Turkey, Ozaslan et al examined 240 patients who had undergone MRM with ALND, and found that lymphedema developed in 28% of the patients. Additionally they found that axillary radiotherapy and BMI increased the risk of developing lymphedema.(2)

In Australia, in a meta-analysis and systematic review by DiSipio et al, they estimated that the incidence of lymphedema on the upper arm post treatment of breast cancer was about 21.4%.(19). They found out that after breast cancer surgery or diagnosis this incidence seemed to increase up to 2 years. In women who had sentinel-node biopsy it was four times less than those who had an axillary-lymph-node dissection. Risk factors of being overweight or obese and extensive surgery (i.e., higher number of dissected lymph nodes, axillary-lymph-node dissection, and mastectomy) had a strong evidence level.

According to Hayes et al, upper extremity lymphedema incidence was about 40%. The risk factors included axillary node dissection or more extensive surgery, older age, and experiencing one or several symptom(s) or complication(s) that are related to treatment at baseline which were associated with an increment in odds of lymphedema formation.(9)

In Asia, Mak et al in China interviewed 202 patients (64). They were studying the patients' life quality of these with upper extremity lymphedema post breast cancer. Their conclusion was that these patients had an inferior quality of life and higher level of arm symptom-related stress and distress.

In Ghana, Sekyere et al studied arm lymphedema incidence and its risk factors resulting from treating breast cancer. 9.9% of the 313 patients they studied developed lymphedema. ALND dissection was a significant risk factor in their population, while BMI and hypertension were not associated with an increase risk(65)

In Kenya, Mbaabu et al, using the DASH assessment of upper arm disability (24), found that axillary surgery for early breast cancer impacted negatively on the patient's life quality. All the 102 participants reported upper arm symptoms/morbidities. These included upper arm heaviness, pain and neuropathy. Most patients suffered from neuropathy and heaviness. They

made a conclusion that after primary surgery there is need for the implementation of targeted rehabilitation services.

2.9: Tools for assessing lymphedema

Several tools have been developed to assess and treat lymphedema, including the Lymph-ICF tool and The DASH questionnaire.

Lymph-ICF tool. The lymphedema functioning, Disability and health questionnaire. It is a descriptive and evaluative tool, used to evaluate the patient's activity limitations, impairments in function, and participation restrictions for those who have undergone breast cancer treatment and have arm edema. In the questionnaire there are 5 sections wit 29 Questions; household activities, mobility services, mental function, physical function, and life and social activities. It has been proven as valid and reliable, though it does not predict the occurrence of lymphedema.(66)

The DASH questionnaire. The Disabilities of the Arm, Shoulder and Hand (DASH). It is self-reported with 30 items that basically assesses the patients' quality of life. It indicates the impairment impact on the type and level of disability hence it assesses the whole ability of a person to function. The items have been grouped with 21 items enquiring about the degree of performance difficulties in the various physical activities due to issues with the hand, shoulder, and arm; five items enquiring about the severity of pain, activity-related pain, stiffness, weakness, and tingling symptoms; and four items enquiring social functioning problems and their impact, self-image sleep, and work. Thereafter, the scores (DASH Score) are used in calculating a scale score that ranges from 0 to 100. 0 shows no disability while 100 is the most severe disability. (24)

2.10: Problem Statement

Breast cancer is the most common cancer in women worldwide. Its management entails different modalities including chemotherapy and surgery.

Attendant upper arm morbidities occur with these management modalities including lymphedema, stiffness, numbness and pain.

This study aims to find out the prevalence and risk factors associated with upper extremity lymphedema post breast surgery in KNH

2.11: Study justification

The incidence of lymphedema varies globally, ranging from 5%-60%. While these figures indicate studies done in the west and in east, we do not know our prevalence and factors influencing the occurrence of lymphedema. The risk factors to developing lymphedema post breast surgery have also been studied. There has been no study to get the real prevalence and hence the burden of lymphedema after breast surgery in our set up. Therefore there is a dearth of data that will guide both the clinical team and policy makers.

The information from this study will be useful especially to the breast surgeons as it will inform the decision to adopt newer ways to prevent this, especially intra operatively and to send patients at risk for early management.

It will also be useful in guiding policy in terms of incorporating physiotherapy as part of breast MDT, and enhance allocation to training and resources aimed at managing the lymphedema.

2.12: Key Research Questions

What is the prevalence and factors associated with upper extremity lymphedema in patients post breast cancer surgery at Kenyatta National Hospital?

2.13: Study Objectives

2.13.1: Broad Objective

To find out the prevalence and risk factors associated with upper extremity lymphedema post breast surgery in KNH

2.13.2: Specific objectives

1. To determine the proportion of patients who developed lymphedema post breast surgery in KNH.
2. To determine the risk factors in the lymphedema patients
3. To establish the association between the risk factors and lymphedema development

CHAPTER THREE: METHODOLOGY

3.1: Study Design

This was a retrospective cross sectional study on records of patients operated on between January 2014 and December 2019.

The study aimed to collect data for patients who were managed in the past. This data was for a defined time, and the patients were not followed up. This was then used to calculate the prevalence of lymphedema.

3.2: Study site

The study was conducted at the Health Information (Medical Records) department at the Kenyatta National hospital, Nairobi Kenya. KNH hospital is the largest referral hospital in Kenya in Nairobi County, with a robust breast clinic where patients are managed in an MDT. Subsequently all the patient information is stored at the Medical Records department where the study will be conducted.

3.3: Study population

Patients who underwent breast surgery between January 2014 and December 2019 in KNH.

3.4: Sample size Determination and Formula

We used the Cochran formula, and calculated the sample size as follows

$$n = \frac{Z^2 p(1-p)}{d^2}$$

Where;

n= sample size

P=expected proportion= 50% (the expected proportion is between 5% to 60%) (1)

d=precision set at 5% Z^2=1.96

Therefore

$n = \frac{1.96*0.5(1-0.5)}{0.05^2}$

Hence n=384

3.5: Sampling Procedure and Technique

A convenient sampling technique was used to select records of patients who meet the selection criteria. The patient files were picked as per convenience/easy availability and retrievable. All

patients between the study periods were recruited until we reached the critical number. Data was then collected from the files and used in the study.

3.6: Recruitment of Study Participants

3.6.1: Inclusion criteria

The participants recruited into the study were:

1. All records for patients who underwent breast cancer surgeries from January 2014 to December 2019 in KNH.

3.6.2: Exclusion criteria

- Patients' medical records that were incomplete.
- Patients with primary lymphedema and non-BCRL.

3.7: Data Variables

Independent variables

- Treatment related factors; ALND, SLNB, adjuvant chemotherapy, neoadjuvant chemotherapy, radiotherapy post mastectomy, number of lymph nodes removed
- Non treatment related factors; Age, pathology of breast ca (invasive/DCIS), axillary recurrence, number of positive lymph nodes, BMI, tumor location in quadrants, presence/ absence of lymphedema.

Dependent variable-lymphedema

3.8: Study Materials

Study materials used for study were stationaries, storage files, flash drives, hard drives and password protected computers.

3.9: Training Procedure

2 Research assistants were recruited among the UON medical undergraduate students. They were trained for 2 weeks on

- maintenance of confidentiality,
- information retrieval from patients' records
- Filling of the questionnaire.

Their proficiency was tested before the start of the actual study.

3.10: Quality Assurance Procedure

The following measures were taken for quality assurance through all the stages of the study.

- The data manager ensured that data obtained from the records were correctly filled and counterchecked. This was done on a daily basis
- Data was stored in password protected computers, hard drives and flash drives that was accessible to only the principal investigator, supervisors and statistician to ensure confidentiality was maintained

3.11:.Data Management and Analysis

Data was collected via a printed questionnaire after obtaining institutional approval. Demographic data as well as clinical data relevant for the study was obtained from the patients' medical records. The data was collected by the Principal Investigator and trained research assistants.

2 Research assistants were recruited among the UON medical undergraduate students. They were trained for 2 weeks on maintenance of confidentiality, information retrieval from patients' records and filling of the questionnaire. Their proficiency was tested before the start of the actual study.

The data that was collected included, the demographics; the diagnosis; radiotherapy post mastectomy; axillary lymph and sentinel lymph node dissection, neoadjuvant and adjuvant chemotherapy, number of lymph nodes dissected, axillary recurrence, tumor location in terms of quadrants, BMI(height and weight) presence and absence of lymphedema.

Prior to data collection ethical approval was sought, thereafter recruitment of research assistants was done to assist in data collection. The research assistants were trained on maintenance of confidentiality, information retrieval from patients' records and filling of the questionnaire.

To maintain confidentiality, all questionnaires did not have identifying features such as names of the patients but a pre-assigned serial number. The questionnaires were then checked for completeness prior to storing them in a secure lockable cabinet only accessible to the PI and the research assistants.

Collected data was sorted, cleaned, categorized, and entered to the statistical software package SPSS version 24 (Chicago) for analysis. The folder containing the data was password-protected and uploaded to a cloud storage drive and back up was done daily to prevent missing entries. Means and standard deviations were used in summarizing and analyzing continuous data while the analysis and display of categorical data was done in charts using proportions and frequencies. Chi-square test and fishers' exact test were used for bivariate analysis, to establish the correlations between presence of lymphedema and clinic-demographic characteristics of

the study population. Analysis of variance (ANOVA) and Independent sample T tests were used to establish association between quantitative and other clinic-demographic parameters. Logistic regression was used at a multivariate level to establish factors that are independently related to development of lymphedema. A P value of less than 0.05 was the cutoff for statistical significance. Data was presented as figures, texts, and tables.

3.12: Ethical Considerations

Prior to commencement of the study, approval was sought from the University of Nairobi Ethical Review committee and Kenyatta National Hospital.

Institutional approval was obtained from the KNH administration to allow access to the patients' records

3.13: Data management

Physical Data sheets were stored in a locked drawer (only the Principal Investigator had a key). This was shredded later. Electronic copies of spreadsheets, clean dataset and exploratory data analysis sheets was deposited in encrypted form into the UoN's research repository for future reference as necessary.

3.14: Study Results Dissemination Plan

Research findings were presented in bound booklets and in electronic forms and disseminated to the department of Research and Programs of Kenyatta National Hospital, Department of Surgery and office of Postgraduate studies of University of Nairobi.

Finally, it will be presented in academic forums in and out of the country as appropriate e.g. Sine Qua Non journal.

3.15: Study limitation and How to Minimize them

Incomplete records as the study was retrospective. This was minimized by excluding all files whose records were incomplete

3.15: Study Closure Plan and Procedure

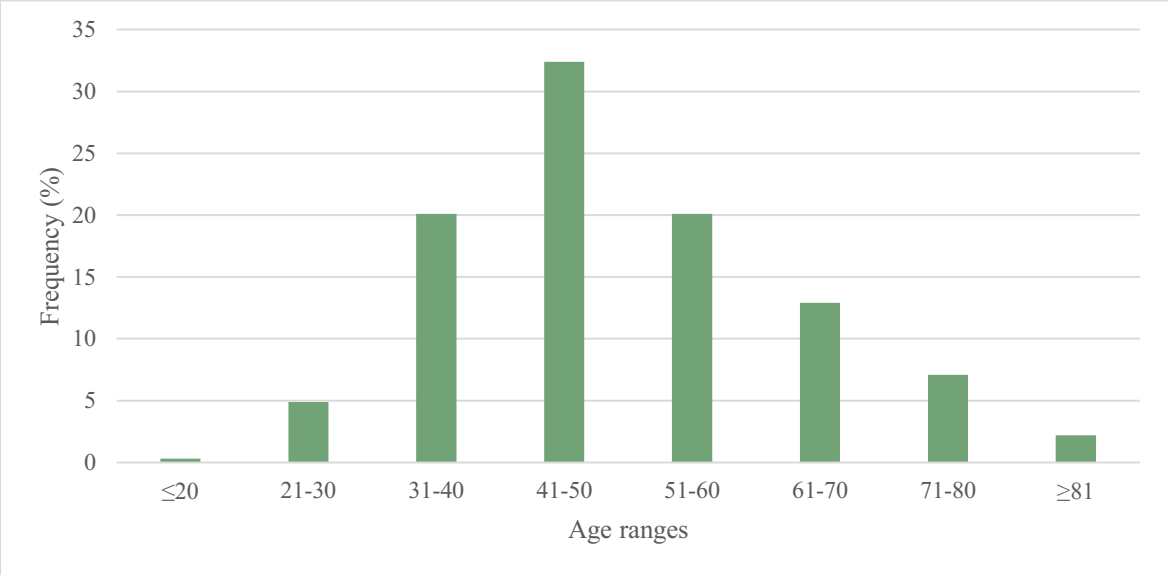
The study was conducted in three phases: phase one entailed recruitment and data collection, followed by data analysis and presentation to the department of Surgery for review. The third phase entailed feedback to the key stakeholders. The recommendations from these feedback sessions was incorporated into the final report before publication.

CHAPTER FOUR: RESULTS

4.1 Demographics

A total of 364 participants were included in the study. Mean age of respondents was 50.5±13.8 years and ranged from 12years to 96years. The majority of the participants were between 41-50 years (table 1)

Table 1: Age vs frequency distribution table



4.2 Patient characteristics pre-surgery

Invasive carcinoma constituted a majority of the diagnoses 343, (94.2%) compared to non-invasive carcinoma, 21(5.7%). The mean BMI of participants was 22.1±2.1 and ranged from 17kg/m^2 to 35 kg/m^2

4.3 Tumor location

Most patients had breast cancer located in the upper outer quadrant (61%) followed by lower outer quadrant (18%). (Figure 6)

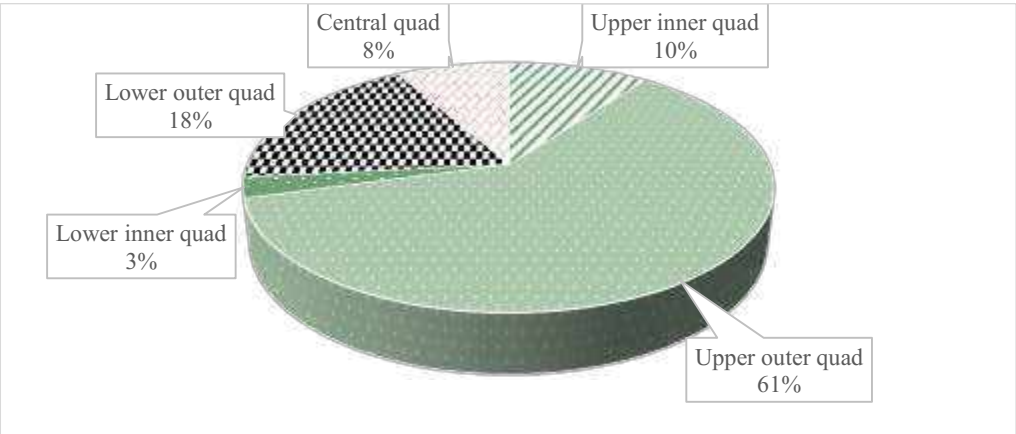


Figure 6: Tumor location

Table 2: Distribution by interventions

Item	Presence	Frequency	Percentage
Neoadjuvant chemotherapy	No	265	72.8
	Yes	99	27.2
Surgery	Wide local excision	11	3.0
	Mastectomy	353	97.0
Lymph node dissection	SLNB	10	2.7
	ALND	354	97.3
Post-operative radiotherapy	No	191	52.5
	Yes	173	47.5
Adjuvant chemotherapy	No	118	32.4
	Yes	246	67.6

4.4 Interventions

Among the patients in the study, 99 patients (27.2%) received neoadjuvant chemotherapy, compared to 265 patients (72.8%) who did not receive. (Table 2)

At surgery, most patient had mastectomy done with 353 patients (97%) Vis avis 11 patients (3%) who underwent wide local excision. On axillary management 354 patients (97.3) had axillary lymph node dissection, while only 10 patients (2.7%) had sentinel lymph node biopsy. (Table 2)

The mean number of nodes removed was 8.4±4.1 nodes ranging from no nodes to 25 nodes.

In the adjuvant set up 191 patients (52.5%) received radiotherapy, with 173 (47.5%) not receiving. A further 246 patients (67.6%) received adjuvant chemotherapy, while 118 patients (32.4%) did not receive. (Table 2)

Table 3: Distribution by complications

Item	Presence	Frequency	Percentage
Axillary recurrence	No	345	94.8
	Yes	19	5.2
Lymphedema	No	338	92.9
	Yes	26	7.1
Lymphedema stage	Stage 1	22	84.6
	Stage 2	4	15.4

4.5 Post-surgery complications

After surgery 19 patients (5.2%) developed axillary recurrence (Table 3). Upper limb lymphedema developed in 26 patients (7.1%) of whom 22 patients (84%) had stage 1 lymphedema (Figure 7)

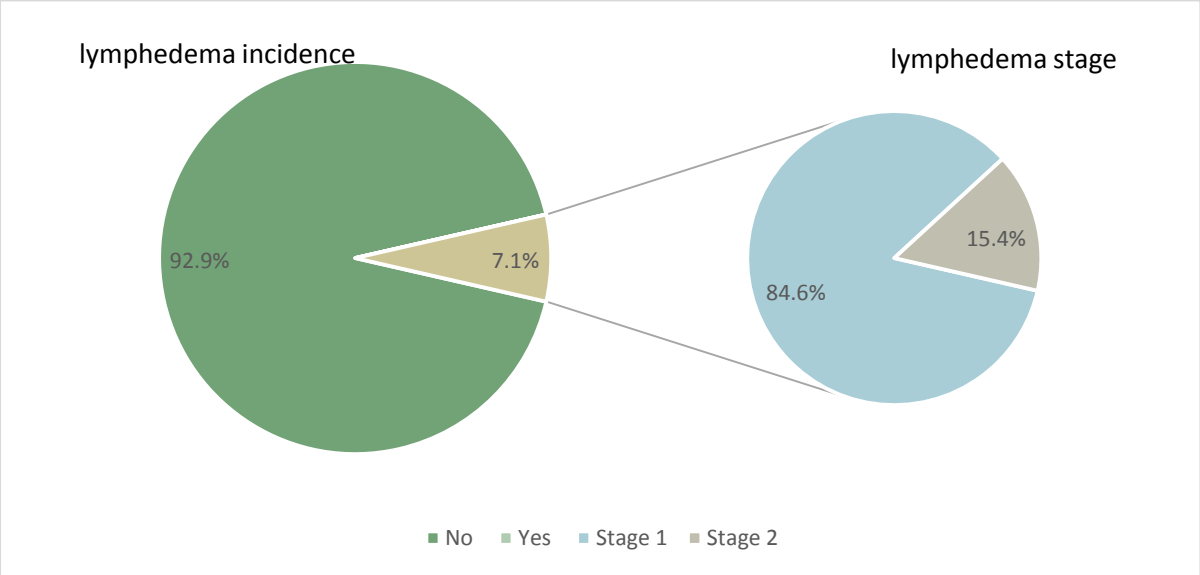


Figure 7: Lymphedema incidence and stage

4.6 CORRELATIONS/BIVARIATE ANALYSIS

4.6.1 PATIENT/DISEASE RELATED AND PRE-OPERATIVE MANAGEMENT FACTORS

4.6.2 Diagnosis, vs lymphedema development

Clinically 96% of patients with lymphedema had invasive cancer, translating to about 7% of all patients with invasive cancer. Of the patients with non-invasive cancer, only 1 out of 14 developed lymphedema, representing 6.7%. This correlated to a likelihood ratio of 0.08 with a chi square coefficient of 0.08. However, with a p value 0.928 this relationship was not statistically significant. (table 4)

Table 4. Bivariate analysis of patient/disease related and preoperative management factors

Variable	Likelihood ratio	Pearson chi square	df	Asymptotic Significance (2-sided) (p value)
Diagnosis	0.008	0.008	1	0.928
Tumor location	2.3	1.675	4	0.795
Neoadjuvant chemotherapy	0.248	0.240	1	0.624
BMI	18.575	25.316	13	0.021

4.2.3 tumor location vs lymphedema development

61% of all tumors were located in the upper outer quadrant. Of these, 7.3% developed lymphedema. With a p value ranging between 0.56-0.99 (upper outer quadrant-0.90, upper inner quadrant-0.56, lower outer quadrant-0.90, lower inner quadrant-0.90), and a chi square coefficient of 1.675, with a p-value of 0.795, this relationship was deemed not statistically significant. (table 4)

4.2.4 Neoadjuvant therapy vs lymphedema development

Even though the patients who had neoadjuvant chemotherapy were a smaller proportion compared with those who did not receive (27.2% vs 22.7%), the proportion of patients that developed lymphedema in each category was similar (6.1% vs 7.5% respectively). This correlated to a likelihood ratio of 0.248 with a chi square coefficient of 0.24. However, with a p value 0.63 this relationship was not statistically significant. (table 4)

4.2.5 BMI vs lymphedema development

The mean BMI of participants was 22.1±2.1 and ranged from 17kg/m^2 to 35 kg/m^2.When analyzed against lymphedema development, the likelihood ratio was 18.6, and a chi square of 25.3. This was statistically significant as the p-value was 0.021 (table 4)

4.3 SURGERY RELATED FACTORS

Table 5. Surgery related factors bivariate analysis

Variable		**Lymphedema Present**		**χ^2**	**OR**	**95% CI of OR**	**P-Value**
		No	**Yes**				
Surgery	Wide local excision	11(100%)	0	00			1.00
	Mastectomy	327(92.6%)	26(7.4%)				
Lymph node dissection	SLNB	10(100%)	0				1.00
	ALNB	319(92.5%)	26(7.5%)				

4.3.1. Mastectomy/WLE vs lymphedema development.

At surgery, most patients had mastectomy done with 353 patients (97%) Vis avis 11 patients (3%) who underwent wide local excision. None of the patients who underwent WLE developed lymphedema. Of the 352 patients who underwent mastectomy 7.4 % (26 patients) developed lymphedema. Since no patient with WLE developed lymphedema, an odds ratio could not be calculated. The calculated p value of 1 meant that the relationship was not statistically significant. However clinically WLE is not associated with development of lymphedema, while mastectomy is.

4.3.2 SLNB VS ALND

On descriptive statistics only 2.7% of patients underwent SLNB, as opposed to a majority, 97.3% who underwent ALND. There was no lymphedema development in the patients who had undergone SLNB. However, the patients who developed lymphedema (26 patients) had all undergone ALND. This shows that clinically, ALND is a big risk factor for development of lymphedema. Since no patient developed lymphedema amongst those who had undergone SLNB, an odds ratio could not be calculated. The p value however was 1, hence this relationship was not statistically significant.

4.4. POST-OPERATIVE MANAGEMENT

Table 6. Post-operative management

Variable		**Lymphedema Present**		χ^2	**OR**	**95% CI of OR**	**P-Value**
		No	**Yes**				
Post-operative radiotherapy	No	182(95.3%)	9(4.7%)	3.4	2.20	1.0-5.1	0.06
	Yes	156(90.2%)	17(9.8%)				
Adjuvant chemotherapy	No	114(96.6%)	4(3.4%)	3.4	2.80	0.94-8.3	0.06
	Yes	224(91.1%)	22(8.9%)				
Axillary recurrence	No	323(93.6%)	22(6.4%)	5.1	3.91	1.2-12.8	**0.02**
	Yes	15(78.9%)	4(21.1%)				

4.4.1 adjuvant radiotherapy vs lymphedema development

Just slightly less than half (47.5%) of total patients underwent post-operative radiotherapy. Of these, 17% developed lymphedema. On the other hand, of the patients who didn't get radiotherapy, only 9% developed lymphedema. The odds ratio was 2.2 (CI 1.0-5.1), with a chi square of 3.4. The p value however was 0.06, hence this relationship was not statistically significant.

4.4.2 Adjuvant Chemotherapy vs lymphedema development

Post operatively, 246 patients (67.6%) received chemotherapy, while 118 (32.4%) did not. On univariate analysis 8.9% of patients who received chemotherapy developed lymphedema while 3.4% of patients who did not receive chemotherapy developed lymphedema. The odds ratio was 2.8 (CI 0.94-8.3) with an X2 coefficient of 3.4. However with a p value of 0.06, this relationship was also found not to be statistically significant.

4.4.3 Axillary recurrence vs lymphedema development

Approximately 5.2% (19) of patients had axillary recurrence. Of these 4 (21.1%) developed lymphedema. On the other hand only 6.4% of patients who didn't have axillary recurrence developed lymphedema. This correlated to an odds ratio of 3.91, with a chi square of 5.1. The p value was 0.02, hence this factor was found to be statistically significant.

4.5. Age vs Lymphedema

There was no significant difference in mean age of participants who developed lymphedema (51.7yrs±16.2) compared to those who didn't (50.4±13.7yrs). With a chi square value of 6.79, and a p-value of 0.431, and a likelihood ratio of 5.803, there was no significant difference between the 2 groups in relation to age.

Table 7. cross tabulation of age vs lymphedema

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	6.979[a]	7	.431
Likelihood Ratio	5.803	7	.563
Linear-by-Linear Association	.001	1	.975
N of Valid Cases	364		

DISCUSSION

Secondary lymphedema in the upper limb following intervention for breast cancer is a common problem whose incidence ranges from 5% to 60% (1)(2)(3)(4). This variation depends on diagnostic criteria, the modality of treatment and duration of the study(5). The study we have done was a retrospective cross sectional study on records of patients operated on between January 2014 and December 2019. From our results, the incidence of lymphedema in patients who have undergone surgery for breast cancer in our set up was 7.1%. (Figure 7).

The likelihood of a person to develop lymphedema is mainly dependent on the individual risk factors of the patient. Generally, these potential risk factors are classified into non treatment-related or treatment-related.

Several studies have looked into the different risk factors and have tried to find out which are the significant factors.

Among the non-treatment related factors that we studied were; Age, pathology of breast ca (invasive/DCIS), axillary recurrence, BMI, tumor location in quadrants.

Armer et al in their paper had found out that women aged younger than 60yrs had a higher likelihood of lymphedema development compared to women older than 60 years(4). In our study, there was no significant difference in mean age of participants who developed lymphedema (51.7yrs±16.2) compared to those who didn't (50.4±13.7yrs) (p=0.431).

It has been shown that the risk of lymphedema is more in invasive carcinoma than in non-invasive carcinoma. Ziping et al found that lymphedema incidence was far higher among patients at the stages T1, T2, and T3 compared with those at stage Tis. Though the incidence

did not significantly differ among the T stages. It was also unrelated to the diseased part of the breast/tumor location (47). However, in our study, with a likelihood ratio of 0.08 and a p value 0.928 this relationship between diagnosis and lymphedema development was not statistically significant. The same applied to the tumor location/diseased part (p=0.795).

The risk factors that were independently significant in our study were BMI and axillary recurrence. The BMI of patients studied ranged from 17kg/m^2 to 35 kg/m^2. When analyzed against lymphedema development, the likelihood ratio was 18.6, and a chi square of 25.3. This was statistically significant as the p-value was 0.021. This has been well studied with researchers like Jammallo et al finding that the independent risk factor for BCRL was when a patient had a BMI equal to or greater than 30 kg/m2 (48). On the other side the axillary recurrence was also found as an independent risk factor (p value 0.02).

The treatment related risk factors that we studied included, type of surgery to the breast and to the axilla, adjuvant and neoadjuvant radiotherapy and chemotherapy.

It is generally accepted that more extensive ALND results in more extensive surgical disruption of lymphatic vessels and, consequently, is associated with an increased risk of lymphedema. This was proven in our study, which showed that all the patients who developed lymphedema had undergone ALND, while none who underwent SLNB. Clinically, this was very significant. Recent data estimated that patients' incidence with unilateral breast cancer who receive ALND is four times more than those who receive SLNB. This suggests that while minimizing the risk of lymphedema in patients with early breast cancer or clinically node negative breast cancer SLNB is an effective option for staging the axilla. (9)(42). However on bivariate analysis, the relationship between lymphedema development and whether the patient had ALND or SLNB was not statistically significant (p=1).

We also studied whether the extent of surgery to the breast had any impact on lymphedema development. Even though mastectomy is more extensive compared to WLE, statistically, these factors were not significant (p=1). However, no patient who underwent WLE developed lymphedema. This could actually be attributed to the fact that in our set up, WLE is mainly done in BCS, and therefore it is usually followed by radiotherapy. On the other hand mastectomy is usually done during MRM, hence followed by ALND.

The effect of neoadjuvant chemotherapy on BCRL risk is still unclear though it has been suggested that neoadjuvant chemotherapy could decrease BCRL incidence by reducing the number of positive lymph nodes(46). The use of taxane therapy has also been hypothesized to cause lymphedema due taxane induced fluid retention. Kilbreath et al in a prospective cohort study found that arm swelling at 6 and 12 months was associated with adjuvant taxane

therapy(45). In our study however, the use of chemotherapy, whether in the adjuvant or neoadjuvant set up was not statistically significant.

We also studied the use of adjuvant radiotherapy post breast cancer surgery. It is well known that postoperative radiation therapy is an additive risk factor to axillary node dissection and it also increases the risk for lymphedema. Kissin and colleagues found that the incidences of subjective lymphedema with axillary node dissection alone and axillary node dissection plus radiation therapy were 7 and 38 percent, respectively(44). In our study however the relationship between adjuvant radiotherapy and lymphedema was not statistically significant (p=0.06)

CONCLUSION

Lymphedema after breast cancer treatment is an important, long term and persistent complication which affects the patient's quality of life. If it is not diagnosed and treated in early period, treatment may be difficult and becomes a chronic disease. Once developed, lymphedema cure rates are very low; therefore it is important to avoid or minimize this condition. This can be done once we identify the risk factors, categorize patients into these risk groups and start preventive measures early.

Our results suggest that the most important treatment and patient-related risk factors for breast cancer-related lymphedema were BMI and axillary recurrence. Clinically it was also noted that all patients who had developed lymphedema had undergone ALND, as opposed to none who had SLNB. Elimination or prevention of these risk factors may reduce the incidence of lymphedema.

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ANNEX

Annex 1: Study Instrument

DATA COLLECTION SHEET

1. CODE …….

2. DIAGNOSIS
   - INVASIVE CA ☐
   - NON INVASIVE CA ☐
3. TUMOR LOCATION
   - UPPER INNER QUADRANT ☐
   - UPPER OUTER QUADRANT ☐
   - LOWER INNER QUADRANT ☐
   - LOWER OUTER QUADRANT ☐
4. AGE ☐
5. NEOADJUVANT CHEMOTHERAPY
   - YES ☐
   - NO ☐
6. SURGERY
   - WIDE LOCAL EXCISION ☐
   - MASTECTOMY ☐
7. LYMPH NODE DISSECTION
   - SLNB ☐
   - ALND ☐
8. NUMBER OF NODES DISSECTED ☐
9. POST OPERATIVE RADIOTHERAPY
   - YES ☐
   - NO ☐
10. ADJUVANT CHEMOTHERAPY
    - YES ☐
    - NO ☐
11. AXILLARY RECURRENCE

- YES ☐
- NO ☐

12. LYMPHEDEMA DEVELOPMENT
    - YES ☐
    - NO ☐
13. LYMPHEDEMA STAGE
    - STAGE 1 ☐
    - STAGE 2 ☐
    - STAGE 3 ☐
14. BMI ☐ Kg/m^2