FACTORS THAT CONTRIBUTE TO FIVE YEAR SURVIVAL OF GALLBLADDER CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL: A RETROSPECTIVE COHORT STUDY

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Research project submitted in partial fulfilment of the requirement for the award of Master of Science in Medical Statistics at the University of Nairobi, December 2018.

DECLARATION

I hereby declare that this project is my original work and has not been presented to this institution or other that we know of.

Dr. Alice W. Maingi ……. Date …….
MBChB (UoN)

CERTIFICATE OF APPROVAL

This project is approved for submission in partial fulfilment for the award of the degree in Masters of Science in Medical Statistics at the University of Nairobi.

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DEDICATION

To the Lord Almighty, in whose names all our steps are ordained.

To my late Dad who is a great hero and succumbed to GBC.

To my entire family for the support and encouragement during my studies.

ACKNOWLEDGEMENTS

I wish to thank my entire family for the support and encouragement they provided during my studies.

In addition, I would like to express appreciation for the support of the University of Nairobi and Kenyatta National Hospital. I would also like to thank those who provided input and advice, including Dr. John Kinuthia of the Kenyatta National Hospital Research Department, Dr. Thaddaeus Egondi of Drugs for Neglected Diseases initiative (DNDi), Nairobi, for their contributions to the development of this project.

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LIST OF ABBREVIATIONS

AJCC American Joint Committee on Cancer

CTC Cancer Treatment Centre

CT Computed Tomography

ESR Extended surgical resection

FDG-PET fluorodeoxyglucose-positron emission tomography

GBC Gallbladder Cancer

KNH Kenyatta National Hospital

LN Lymph node

MRI Magnetic resonance imaging

MR Magnetic Resonance

PET Positron emission tomography

SEER Surveillance, Epidemiology, and End Results (SEER)

SOPC Surgical Outpatient Clinic

TNM Tumor Node and Metastasis

UGC unsuspected Gallbladder cancer

US Ultrasonography

DEFINITIONS OF TERMS

Malignancy: Cancerous growths. It is often resistant to treatment, may spread to other parts of the body and sometimes recur after it is removed.

Tumor: A swelling of a part of the body, caused by an abnormal growth of tissue, whether benign or malignant.

Gallbladder: The small sac-shaped organ beneath the liver, in which bile is stored after secretion by the liver and before release into the intestine.

TNM Staging of cancer: The TNM system, each cancer is assigned a letter or number to describe the **tumor**, node, and metastases. T stands for the original (primary) tumor. N stands for nodes. It tells whether the cancer has spread to the nearby lymph nodes. M stands for metastasis.

Chemotherapy: The treatment of disease by the use of chemical substances, especially the treatment of cancer by cytotoxic and other drugs.

Radiotherapy: The treatment of disease, especially cancer, using X-rays or similar forms of radiation.

Neoadjuvant therapy: -In contrast to, is given before the main treatment.

Adjuvant therapy: -Applied after initial treatment for cancer, especially to suppress secondary tumor formation.

ABSTRACT

Introduction: Gallbladder cancer (GBC) is an uncommon malignancy of the biliary tract with a poor prognosis frequently presenting at an advanced stage. Generally, GBC is the most aggressive of the biliary tract cancers accounting for 80-95% of this malignancy's. In addition, it has the shortest median survival duration. Early diagnosis is crucial for improved prognosis. However, indolent and non-specific clinical presentations with a paucity of pathognomonic radiological features often preclude accurate recognition of GBC at an early stage. There is limited documented evidence on the survival and associated factors to guide effective management of GBC patients at KNH.

Objectives: This study aims to determine five-year survival and associated factors leading to death of gallbladder cancer patients seen at KNH

Methodology: The study was a retrospective cohort study of all patients who had a diagnosis of primary GBC and were seen at KNH. The sample size was all patients diagnosed with GBC seen at KNH. Data collected was age, sex, time of diagnosis (pre-op, intra-op), stage of cancer, type of cancer and treatment (surgery, chemotherapy, radiotherapy) given to the patients and it was abstracted from patients' records. Data was analyzed using STATA version 15. Cox regression approach was used to evaluate these factors.

Results: The median survival time for GBC patients is 7.29 months with an interquartile of 2.4-36.75 months. The incidence rate of death among these patients was 7% in a month. There was no significant difference between the predictor variables of age (p=0.769), gender (p=0.548), time of diagnosis (p=0.742), type of GBC (0.494), advanced stage (p=0.813), treatment (p=0.063) on time to death. However, those with advanced stage had a 12%more chance of dying. Participants who underwent surgery and chemotherapy survived longer.

Conclusion: The study established that there was no statistical difference on the predictor variables to time to death on GBC patients. However, late diagnosis leads to finding the malignancy already in its advanced stage hence curative surgery not possible. Consequently, patients who underwent combined treatment of surgery and chemotherapy management had a longer survival.

CHAPTER ONE

1.0 INTRODUCTION

Gallbladder cancer (GBC) is an uncommon yet an aggressive form of gastrointestinal cancer.[1] Unfortunately, the prognosis is always poor. However, it is the commonest malignancy representing 80-90% of cases arising from the biliary tract.[1,2,3] Furthermore, symptoms are vague therefore an early diagnosis is often missed. Diagnosis frequently occurs at an advanced stage of the disease giving it an unfathomable prognosis.[3] Usually, a 5 year survival rate is less than 5% for the more progressed stages.

Incidence rates vary widely among different geographic areas and ethnicities. Extreme cases are reported in South and North American Indians (especially Chilean Mapuche Indians.[4] Other high-risk regions are Eastern Europe, Northern Indian especially in Delhi and South Pakistan. Israel and Japan have a lower rate. In China, incidences have been on the rise and have doubled over the past 20 years especially in Shanghai. Other parts of the world have a significantly lower rate (<2/100,000).

GBC affects women 2 to 6 times more than men and the incidence increases with the age.[2] Majority of patients are diagnosed in their 50's and 60's. However, the last decade has seen a change in this trend as the incidence rates are now lower in this age group and has seen an increase in younger patients.[5] In Kenya the peak age is 51 to 55 years with a mean age of 52 years with a female to male ratio been (2:1).[13]

GBC has no specific cause however, risk factors for the disease provide insight into the pathogenesis for its ethnic and geographic variances. One of the common characteristics is chronic gallbladder inflammation and presence of gallstones. Other risk factors include; Porcelain gallbladder (chronic inflammation), anomalous pancreaticobiliary duct junction, a rare congenital malformation of the biliary duct and gallbladder polyps.

The clinical presentation of GBC is nonspecific making it difficult to diagnose. One of the common signs for early stage carcinoma mimic cholecystitis with upper abdominal pain.[10] Other symptoms include weight loss, fever, jaundice, anorexia, nausea, vomiting, pruritus and abdominal distension mass.[9] The most common physical findings are abdominal tenderness, jaundice, hepatomegaly, pallor, palpable gallbladder, fever and ascites.[9]

Majority (75%) of the diagnosis is discovered during operation with no prior suspicion of GBC.[9] The correct diagnosis of GBC preoperatively is made in 8.3% of the patients. Ultrasonography is the cornerstone for detecting GB pathology by detecting GB wall thickening and mass.[13] Other imaging diagnostics can be used including fluorodeoxyglucose-positron emission tomography (FDG-PET), Magnetic resonance imaging (MRI), Positron emission tomography (PET).

Cancer staging is a fundamental aspect for the preferred cancer treatment and evaluation of cancer therapies. GBC is primarily staged during surgery and the staging is determined by the depth of invasion, involvement of lymph nodes, extension into adjacent organs or structures and metastasis to distant organs or structures.[10] Approximately 85% of GBC accounts for adenocarcinomas and they are usually well or moderately differentiated while adenosquamous, squamous or undifferentiated carcinomas account for the remaining 15%. Less than 1% represents lymphomas or neuroendocrine carcinomas of all GBCs.

Surgery is the only curative therapy for GBC and a mere 25% of cancers are resectable. An early disease leads to a curative resection with a 5-year survival rate of over 95%.[3] Combination of chemotherapy cisplatin-gemcitabine increase the survival of the patients with median survival of 11.7 months compared with gemcitabine alone at 8 months.[13] Radiotherapy and surgery is associated with prolonged survival.[5]

Minimal studies have been conducted in Kenya and Africa on GBC. This study will therefore look at the factors that contribute to death of patients diagnosed with GBC and if there is any comparison with the rest of the world in survival with the poor prognosis.

2 CHAPTER TWO: DEFINITION OF THE PROBLEM

2.6 Problem statement

GBC is a rare malignancy with poor prognosis which is often diagnosed intra-operatively. The symptoms are non-specific and therefore easily missed during the early stages. However, with an early diagnosis there is a better survival rate with curative surgery, adjuvant radiotherapy and chemotherapy treatments. This study therefore seeks to determine the survival of primary GBC patients seen and treated at KNH and the factors that may be leading to death.

2.7 Study justification

GBC is an aggressive, uncommon and poor prognosis malignancy. Currently, in Kenya there is limited evidence-based information on GBC that can guide on diagnosis and treatment of GBC.

This study aims to understand survival of this GBC patients and factors contributing to death in Kenya. This is a malignancy that is quite fatal and not much study has been conducted in Kenya to learn about it. We will seek to understand if the malignancy is diagnosed early, whether intra-operatively or during routine checkup, the staging and histological type and what type of treatment is given to the patients and how these factors contribute to the death of the patients.

This study will contribute towards the knowledge and information on GBC in Kenya. This will in turn contribute towards policy formulation on protocol and guidelines of GBC management. In addition, this study will contribute towards understanding GBC distribution and outcomes in Kenya.

2.8 Broad objectives

To determine the five-year survival and associated factors leading to death of gallbladder cancer patients seen at KNH.

2.9 Specific objectives

1. To determine five-year survival rate of patients diagnosed with gallbladder cancer at KNH.
2. To determine factors (demographic, clinical and treatment) associated with survival of patients diagnosed with gallbladder cancer

2.10 Research questions

1. What is the five-year survival rate of gallbladder cancer patients?
2. How does the GBC staging at diagnosis affect survival?
3. How does the histology type of the GBC affect/ influence the survival?
4. How does mode of diagnosis (intra-op or before surgery) influence the survival?
5. How does mode of treatment(surgery/chemotherapy/radiotherapy) influence survival of GBC patients.

3 CHAPTER THREE: LITERATURE REVIEW

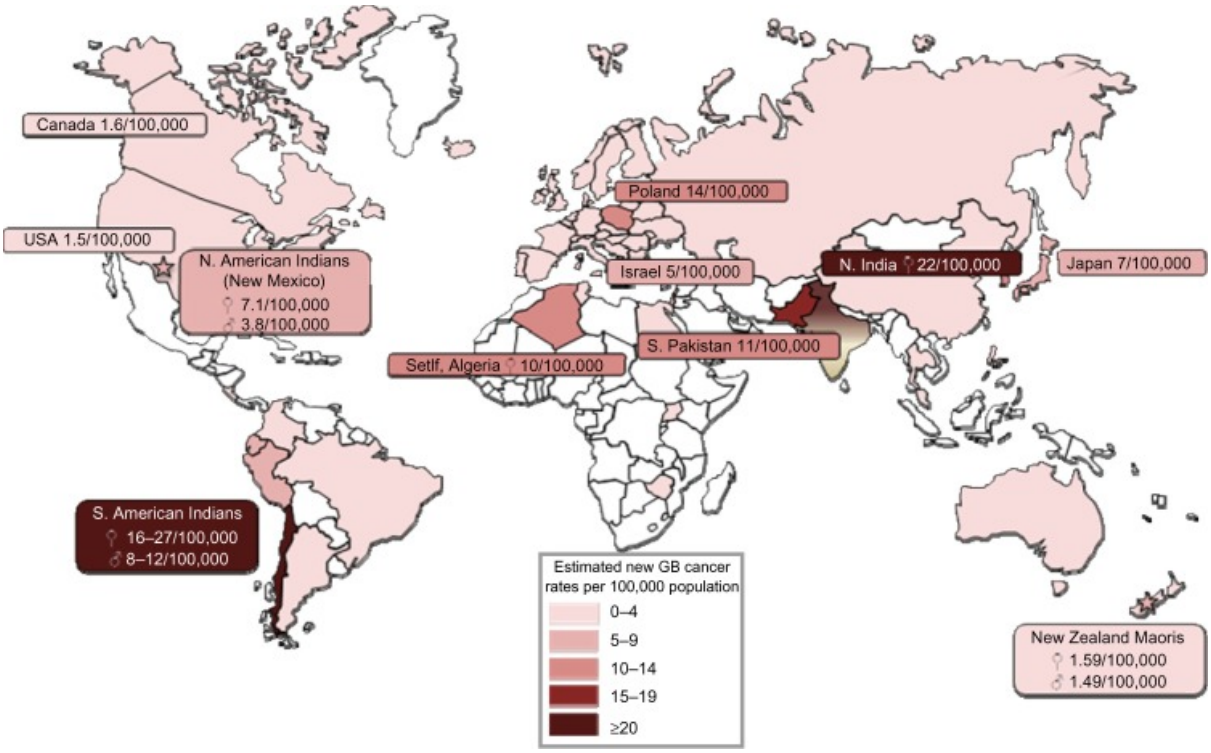
Gallbladder cancer (GBC) is an uncommon yet an aggressive form of gastrointestinal cancer.[1] Unfortunately, the prognosis is always poor because the prospects of prevention still remains a challenge. However, it is the commonest malignancy representing 80-95% of cases arising from the biliary tract.[1, 2, 3] Furthermore, symptoms are vague therefore an early diagnosis is often missed.[3] Anatomically, the gallbladder does not have a serosa to limit the carcinoma from spreading. This carcinoma therefore progresses quietly and usually with a delayed diagnosis thus making it lethal. The late diagnosis frequently occurs at an advanced stage of the disease giving it an unfathomable prognosis. Usually, a 5 year survival rate is less than 5% for the more progressed stages. GBC remains a threatening cancer with a bleak outcome despite the advancement in treatment options; biomedical, technological, surgical, and chemotherapeutic.[1]

1.1 Incidence

Incidence rates vary widely among different geographic areas and ethnicities. Extreme cases are reported in Northern and Southern American Indians (especially Chilean Mapuche Indians).[4] The incidence increases with age and is more common in Caucasians than Africans.[2] Over the last decade, the prevalence of GBC has significantly decreased in the elderly (>50 years) with an increased prevalence in younger patients.[5]

The figure below shows the geographical distribution and incidence rates as per the regions.

1.2 Figure 1



Gallbladder cancer incidence in the world.

Note: Gallbladder cancer incidence rates are highest among certain ethnicities, particularly South American Indians and East Indian (northern India) females. Statistics derived from Cancer Incidence in Five Continents, Vol IX.10 This figure is adapted with permission from Stinton LM, Shaffer EA. Epidemiology of Gallbladder Disease: Cholelithiasis and Cancer. *Gut Liver*. 2012; 6(2):172–187.[3]

1.3 Geography/Ethnicity

There is a varying geographic distribution for GBC. The prevalence rates are unusually high in Latin America (Chile, Bolivia, Columbia) and Asia (India, Korea, Japan & Pakistan), comparatively high in some countries in Central and Eastern Europe (e.g. Germany, Slovakia, Czech-republic, Hungary, and Poland). In addition, fewer cases have been reported in the USA and most western and Mediterranean European countries i.e United Kingdom, Norway , and France.[3] It is comparatively rare in other parts of the world e.g. Australia.[6] Certain ethnic groups are identified as high risk and this include Hispanics, American Indians and Mexican Indians.[6]

1.4 Age and Sex

The incidence increases with age. GBC is more common in the female gender and also risk increases with age.[8] Age at diagnosis is in the 5th and 6th decades.[9] Median age is 67 years (range 28-100).[7] In Kenya the peak age incidence for patients with cancer is 51 to 55 years, with a mean age of 52.0 years (range 27 - 82 years). 62.5% of the patients are above 51 years.[13] the female gender shows a notable difference in the number of GBC cases reported worldwide. The studies have shown that women are more vulnerable to the disease as compared to men, especially in Asian (Indian, Pakistan), and in Native American females. [2, 3]

The ratio of women to men affected by the disease is 2:6 [2,3] with 27.3/100,000 for females and 12.3/100,000 for males.[3]Another study found GBC to be more common among women 1.4 case per 100,000 than men 0.8 cases per 100,000. All populations have similar findings with the rates being three times higher in females[4, 5]the statistics in Kenya are not different from other parts of the world with a 2: 1. female to male dominance.[13]

1.5 Risk factors

GBC has no specific cause however, risk factors for the disease create awareness into the pathogenesis for its ethnic and geographic discrepancies. One of the common characteristics is chronic gallbladder inflammation and presence of gallstones. Furthermore, Cholelithiasis is present in approximately 85% of patients diagnosed with GBC. People with a high prevalence of gallbladder carcinoma also have an excessively elevated occurrence of cholesterol of gallstone disease. The connection with cholelithasis may give insight into why the female gender, multi-parity or a high body mass index are also associated with a high risk of GBC.[20]

Other risk factors include; Porcelain gallbladder (chronic inflammation) that may lead to calcium deposit formation in the gallbladder incidence is low (<1%), anomalous pancreaticobiliary duct junction, a rare congenital malformation of the biliary duct. It is more common in Asians (especially Japan) 3-18 % of patients with this anomaly are likely to develop GBC. Gallbladder polyps are also considered a risk factor accounting for 5% of adults (range 0.3-7%) but this percentage depends on population studied.[20]

3.6 Signs and Symptoms

The clinical presentation of GBC is indefinite or delayed comparative to pathologic advancement, thus progressing to advanced stage of the disease whose prognosis is always poor. Symptoms are vague and may include: upper abdominal pain, jaundice, weight loss and

fever.[10] Less common symptoms may include: pruritus, nausea, vomiting, anorexia, weight loss, and abdominal distension mass.[9] Majority of the patients present with advanced disease. 87.5% of the patients have symptoms for less than one year. The most common physical findings are abdominal tenderness, jaundice, hepatomegaly, pallor, palpable gallbladder, fever and ascites. [9]

3.7 Diagnosis

The clinical presentation of GBC is nonspecific making it difficult to diagnose. However, the carcinoma may be discovered early, as a secondary finding during cholecystectomy for symptomatic cholelithiasis or late when the tumor has metastasized or ravaged the bile duct. [20] In the majority of patients (75%), the diagnosis is established at operation with no preoperative suspicion of the diagnosis.[9] Additionally, another study, found that 47% of cases are discovered incidentally at routine laparoscopic cholecystectomy.[7] Moreover, 40% of patients are diagnosed at an advanced stage.[8]

In addition, 43% of GBC cases are diagnosed when the carcinoma has spread to adjoining structures or lymph nodes and 42% of cases are after metastasis to distant organs or lymph nodes [11]. In 16.7% of the patients the diagnosis was first made by the pathologist during cholecystectomy for presumed benign disease. A third of the patients with gallbladder cancer have exploratory laparotomy and biopsy only.[9]Early diagnosis of gallstones and treatment (surgical removal of gallbladder) is at present preventive measure that can be taken to control GBC.

However, other interventions like those used to control or prevent obesity, cholecystitis and gallstone formation should be assessed.[12] Lack of proper diagnosis at early stages of the disease, and inadequate routine screening tests leading to early detection are partly responsible for the poor prognosis of this disease.[2]The correct pre-operative diagnosis of gallbladder cancer is made in only 8.3% of the patients.[9] Ultrasonography (US) evaluation plays a major role in detecting gallbladder (GB) pathology. US reveals the presence of abnormal GB mass or wall thickening. Furthermore, a positive result may also show invasion to structures in proximity, vascular invasion, lymphadenopathies, dilatation of the biliary and ascites.[13]

In the presence of gallstones (GS), acoustic shadowing may be a hindrance to the radiologist. Therefore, focus should be on the GB wall to detect abnormal lesions.[13] Findings through US may be suggestive of GBC. However, the results may be inconclusive and therefore an FDG-PET should be considered a secondary test to establish the benign or malignant nature of the

lesion and acquire a primary staging study. Whenever a positive diagnosis of GBC is confirmed, further test are carried out; thin-slice spiral CT to furnish useful information on local spread.[10]

Magnetic resonance imaging (MRI) is the most effective mode of screening in detecting hepatic, vascular and biliary invasion. Together with magnetic resonance angiography (MR), MRI gives accurate details concerning resectability. Positron emission tomography (PET) is a test that shows imaging modality where the tumor cells reveal an uptake of fluorodeoxyglucose. The findings of this test are essential in differentiating a disease that is benign and that which is malignant in the preoperative phase. PET is preferred over CT in investigating lymph nodal involvement and distant metastasis.[13]

3.8 Staging of GBC

GBC is staged according to the depth of penetration and area it has spread to. [10] The carcinoma is primarily staged from surgical exploration or resection. However, not all GBC patients undergo surgery prior to findings therefore a single TNM classification will be used for both pathological and clinical staging.

The figure below shows tumor invasion and the degree of spread.

3.9 Figure 2

Primary tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades the lamina propria or muscle layer
T1a	Tumor invades the lamina propria
T1b	Tumor invades the muscle layer
T2	Tumor invades perimuscular connective tissue; no extension beyond the serosa or into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Regional lymph nodes (N)

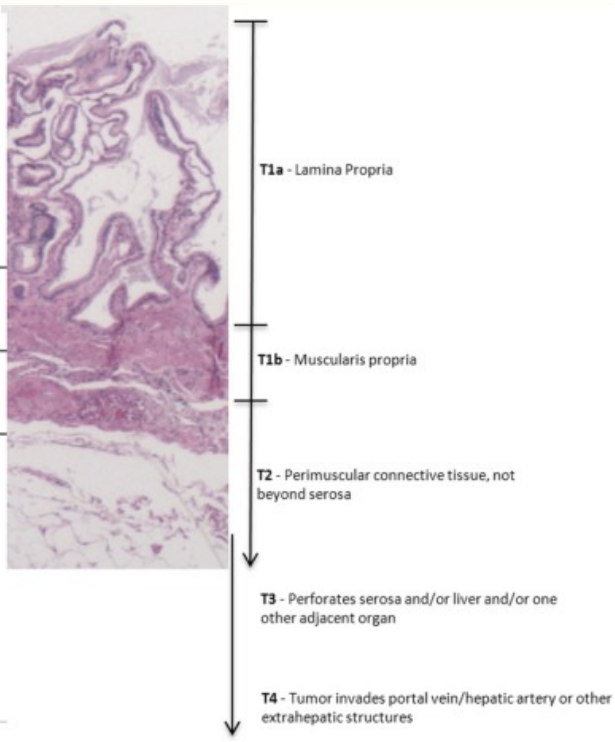
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1



GBC staging and histology.

Notes: Histology courtesy of Dr S Urbanski, Department of Pathology, University of Calgary. Tumor invasion (T) largely drives the staging criteria for gallbladder cancer. Regional lymph nodes (N) and distant metastasis (M) further advance staging and worsen the overall prognosis.

According to SEER histological staging localized tumor was (23.7%), regional was (37.4%), and distant was at (38.9%) for the patients.[5]

According to the American Joint Committee on Cancer (AJCC) T1 of the disease, tumor invades the lamina propria or the muscle layer. T2 involves perimuscular connective tissue usually with no invasion past the serosa or liver. T1 to T3 tumor invasion with any nodal involvement is classified as T2.[3] Patients' in T1 account for 5% of all cases recorded in SEER.[14] The deeper the invasion the higher the metastatic rates. Advancement from T2 to T4 tumors adds the possibility of distant metastasis from 16%–79% and the risk of nodal involvement from 33%–69%. Tumor perforation is enhanced by the absence of serosa adjoining to the liver thus enabling hepatic involvement and this qualifies as a T3 tumor. T4 tumors involves blood vessels (hepatic artery or main portal vein) or numerous distant organs or structures. T4 patients' require palliative because the disease has spread beyond treatment options. [3] AJCC rates T4 tumors at 36.6%.[7] In Kenya most patients present with advanced disease.[13]

3.10 Histological type

The histological types are: 88% adenocarcinoma, 4% squamous, 3% neuroendocrine, 2% sarcoma.[7] Adenocarcinoma accounts for 98% of cases making it the most common of all the gallbladder carcinomas. About two third of the cases are fairly or poorly differentiated. Other subtypes are adenosquamous, squamous, mucinous, papillary. [3] according to the histologic classification, Stage I disease accounts for 26.4%; a further 62% with papillary carcinoma were noted to have stage 1 as well.[14]

3.11 Treatment

Total surgical resection remains the preferred choice for curative treatment. Treatment options depend on the stage at which the patient presents. Moreover, early diagnosis and cholecystectomy usually has better outcomes.[3] Stage I and II resection is possible with a good prognosis. Stage III & IV the disease has spread to adjacent and distant areas and ordinarily indicate a locally unresectable carcinoma.[3]An early diagnosis will have a better curative resection (termed “R0 resection”) as tumor invasion is limited to the mucosa or submucosa. Patients in this category usually have a 5-year survival rate.[3]

Un-fortunately due to late diagnosis only about 10% of patients qualify for curative surgery [2]. Neoadjuvant chemo/radiotherapy confers survival benefits in GBC.[17] Patients who have undergone surgery have a significantly higher median survival rate (8 versus 2 months, $P < 0.0001$). Furthermore, surgery in combination with radiotherapy increases survival rates for patients with regional and distant spread but not carcinoma that confined.[5]Radiotherapy treatment has seen patients undergoing surgery reduce.[5]Laparoscopic cholecystectomy is useful for T1 patients.

Extended surgical resection, LN excision, or both may enhance survival rates in patients that have an incidentally diagnosis of GBC. [17]A recent study showed that combining gemcitabine and cisplatinum is now the standard of care for GBC.[13]Patients treated with cisplatin–gemcitabine, median survival was 11.7 months, compared to 8.1 months patients in the gemcitabine. The median progression-free survival is 8.0 months in the cisplatin–gemcitabine and 5.0 months with gemcitabine only.[13]The Kenya National guidelines for cancer management, commonly used chemotherapy is cisplatin and 5-fluorouracil as the preferred first line treatment for non-curative resection malignancy. Gemcitabine and oxaliplatin are also used.[17]

3.12 Mortality

GBC being a lethal disease, early diagnosis is crucial as survival is dependent on it. Sadly, many patients are diagnosed when the carcinoma has already spread and treatment options are limited. Majority of the patients only qualify for palliative care and even those that may undergo surgery, the prognosis is always poor.[3] However, not all is lost as the last decade has seen an increase in the number of patients that survive.[5] Countries with high gallstone incidences usually have elevated mortality rates arising from GBC. A five year Survival rate is at 5% with majority of patients having a 6 month mean survival rate. [3]

Countries with the highest mortality rate include: South American Indians; Bolivian natives, Chilean Mapuche Indians and Chilean Hispanics 3.5 -15.5 per 100,000. Intermediary rates, 3.7 to 9.1 per 100,000, are found in Ecudor, Colombia, Brazil and Peru. Low mortality rates are found in North America, with an exception of American Indians in New Mexico (11.3 per 100,000) and among Mexican Americans.[4] Two-thirds of deaths occurred among women[11] with a mortality rate been 0.7 deaths per 100,000 and men been 0.5 deaths per 100,000.[4,5]

Elderly patients (>60 years), patients with positive LNs involvement and those with advanced disease have a decreased survival rate. Higher survival rates are noted among females and patients undergoing ESR.[16] Female patients with stage IVA with well differentiated adenocarcinoma, have had surgery and radiotherapy have a longer survival rate.[18]
There is a statistically significant (P< 0.00001) linear association between stage of disease and survival time, with survival decreasing as stage increases.[14]
68% of these patients with stage 1 die in the first year. Almost 96% of patients with Stage IV and 87% with Stage 111 disease die in the first year. [14]The higher survival rate of patients with papillary carcinoma correlated with the stage of disease.[14]
The deeper the tumor invasion to the gallbladder layers the worse the prognosis. In fact, the 5-year survival rates range from 70% with involvement of the subserosa, falling to 0% with the spread to adjacent organs.[3]
For patients whose tumor is limited to the gallbladder at the time of surgery, the 2-year survival rate was 45% and the 5-year rate was 32%.[2]

SEER median survival for localized tumor is 20 months, regional 5 months, and distant 2 months.5 while the survival rates for T1, T2 and T3 stages was 100%, 75% and 0% for the patients respectively. [15]

On unsuspected gallbladder cancer, the median survival was i) 12.9 months for stage Ia-III disease ii) 5.8 months for stage IV disease iii) 15.7 months for those discovered incidentally at laparoscopic cholecystectomy iv) 23.4 months for those who received adjuvant therapy[7]. The survival rate for Stage I-II disease was at 65% as compared to zero (0%) for Stage IV disease over a period of five (5) years.[19]

A quarter of the patients with GBC die within the first month postoperatively, whereas only 4.2% of the patients are still alive and on follow-up one year after the diagnosis of cancer.[9]The 5-year survival rates start at 80% for stage 0, then progressively fall to 50% for stage I, 28% for stage II, 8% for stage IIIa, 7% for stage IIIb, 4% for stage IVa, and finally, 2% for stage IVb.3Even in patients undergoing aggressive surgery, 5-year survival rates are 5–10% for gallbladder cancer.17 In fact, the overall mean survival rate for patients with gallbladder cancer is 6 months, with a 5-year survival rate of 5%. [3]

4 CHAPTER FOUR: METHODOLOGY

Study design: This was a retrospective cohort study among patients diagnosed with primary GBC at KNH.

Study Area: The study location was in Kenyatta National Hospital. Patients with GBC were managed at the Surgical out-patient clinic (SOPC). Once they presented with clinical symptoms of gallbladder disease they got investigated and a proper diagnosis was made. Staging of GBC and typing it was made to determine if the patient woulod undergo surgery or palliative treatment. The patients got admitted to the surgical wards with the diagnosis of GBC if it was resectable, and they underwent surgery. Following surgery, some underwent adjuvant chemotherapy and radiotherapy or palliative care. The patients were followed up at the (SOPC) and CTC clinics.

Study population: All adult patients treated at KNH with primary GBC from 2009-2018 and who meet eligibility criteria.

Inclusion criteria:

1. Age $\geq$ 18 years. This is because in the literature review there were no cases of GBC in anyone who was under 18 years.
2. Primary tumor in gall bladder
3. GBC Histologically confirmed

Exclusion criteria:

"0" months survival

4.6 Sample size

All patients treated at KNH with GBC from 2009 -2018 who meet eligibility criteria were included in the study. Patients diagnosed with GBC were few and the total number of patients seen and met the eligibility criteria in the 10-year duration were include in the study. The sample size were patients seen in a duration of 10 years. Hence sampling was not necessary but the power for the study with observed events was established.

4.7 Variables

The dependent variable or the response variable was death of patients with GBC.

The explanatory variables or predictor variable which are called covariates, were the variables which affected survival. The variables assumed to affect survival were age, sex, geographical distribution, time of diagnosis (pre-op or intra-op), staging of GBC, type of GBC and treatment offered (surgery, radiotherapy, and chemotherapy).

4.8 Data management

Data was abstracted from patient files using structured questionnaires. This was be collected by research assistants who were trained on what to collect.
Data was entered into epi data and verified for consistency against the questionnaires.

Data was entered into an epi data and imported to STATA 15 software. Coding, cleaning and analyzing was then done. Cleaning was done by checking for presence of extreme values and missing values. Extreme values the data was confirmed with data on questionnaires. Missing values proportion of missing values was calculated. Results were displayed using tables and figures.

Data protection: Data was entered into epi data and stored safely in the computer which was password protected. It was stored in a password-protected digital format and patient information was de-identified.

4.9 Data analysis

The study focused on time to event which is time to death. Hence the most appropriate method of this study was survival analysis. Survival analysis was used in this study to understand the five-year survival of patients diagnosed with GBC at KNH. Cox proportional hazard regression and Kaplan Meier models was used for analysis.

Survival curves were calculated by the Kaplan-Meier method.
Cox regression was used to assess influence of disease stage, histology type, mode of diagnosis and treatment on survival rate controlling for demographic variables. The method was used to investigate the effect of several variables upon the time a specified event (death) takes to happen. Dependent variable will be time to death.

The explanatory variables or predictor variable which are called covariates, are the variables which affected survival. The dependent variable or response variable was death of patients with GBC.

4.10 Strengths and limitations of the study

i. This study was among the few which have been conducted on GBC and published in Kenya.
ii. There was no follow through of patients by the hospital. Once a patient got discharged by the hospital, they may have decided not to come back to the hospital for follow up or were followed up in a nearby facility hence not coming back to KNH or they may have died. The hospital may not have a mechanism of having a follow up of the patients diagnosed with GBC and hence may be a limitation on knowing the outcome of patients discharged and not come back for review.

iii. The study been a retrospective study, some information was missing in the patient's files.

5 EXPECTED OUTCOMES

To understand if age, sex, mode of diagnosis, staging, type of GBC and treatment have an influence on the survival of GBC patients in Kenya.
To understand if GBC in Kenya has a similar outcome as the rest of the world or it is unique.

6 ETHICAL CONSIDERATIONS

Ethical clearance was sought from Kenyatta National Hospital Ethics and Review Committee (KNH/UON ERC). Authorization was sought from the Hospital to use the data. It was then submitted for approval by research department, KNH and results were presented to KNH. Confidentiality was maintained strictly at all times and no personal identifier information was collected. Data was stored in a password protected computer database. Information was collected from health information records hence no human participants risk or harm was anticipated.

7 RESULTS

1. Characteristics of the sample

We enrolled 49 participants for this study. The mean age was 57 with a standard deviation of 12. Majority of them were female 27 (55%) and over three quarters of the participants were married 35 (76%). A significant number of cases are seen in Muranga been in the lead at 22.4% and Kiambu been 16.3% and Nairobi been at 12.2%.

Table 1:Demographic characteristics

		n	%
Age mean (std dev)		57 (12)	
Gender	Male	22	44.9
	Female	27	55.1
Marital status	Single	6	13.0
	Married	35	76.1
	Divorced	0	.0
	Separated	1	2.2
	Widowed/Widower	4	8.7
County	Unknown	2	4.1
	EMBU	2	4.1
	KAJIADO	2	4.1
	KIAMBU	8	16.3
	KIRINYAGA	2	4.1
	KISII	1	2.0
	KITUI	1	2.0
	MACHAKOS	2	4.1
	MAKUENI	3	6.1
	MERU	2	4.1
	MIGORI	2	4.1
	MOMBASA	1	2.0
	MURANGA	11	22.4
	NAIROBI	6	12.2
	NYANDARUA	1	2.0
	NYERI	3	6.1

Majority of the patients presented with jaundice 79.6%, abdominal pain 77.6%, abdominal distension 57.1% and vomiting 51%. Very few patients came with symptoms came with nausea and fever at 12%. Of the signs jaundice was at 67.3%, abdominal tenderness 51%,pallor and palpable GB were both at 32.7%.The rest of the symptoms were fever and ascites at 18.4% and 28.6% respectively. These is represented in the tables 2 and 3 below;

Table 2:Symptoms

	N	%
Abdominal pain	38	77.6
Weight loss	20	40.8
Fever	6	12.2
Jaundice	39	79.6
Pruritus	21	42.9
Nausea	6	12.2
Vomiting	25	51.0
Anorexia	16	32.7
Abdominal distension	28	57.1

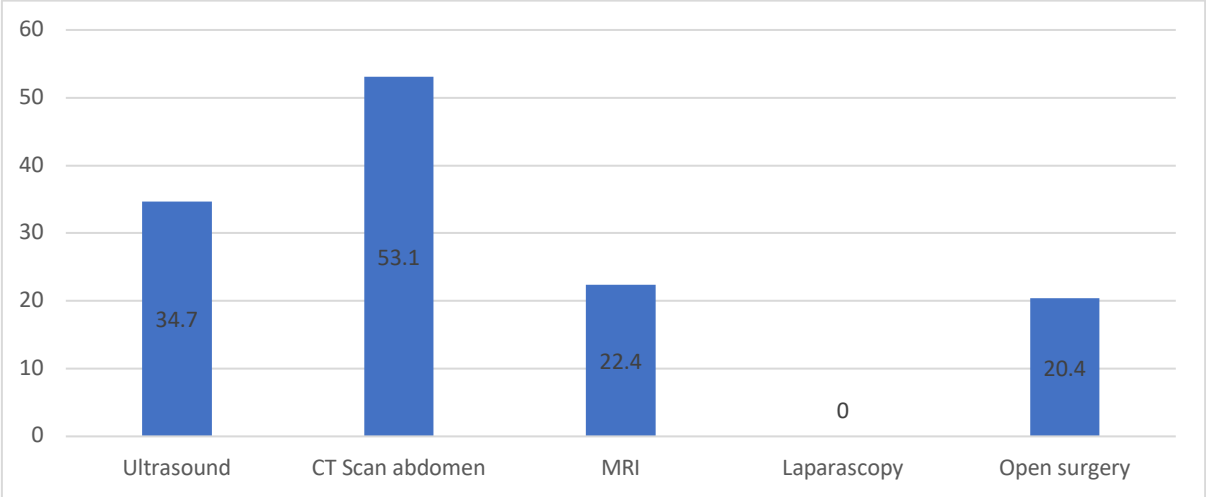
Table 3:Signs

	N	%
Abdominal tenderness	25	51.0
Jaundice	33	67.3
Hepatomegaly	13	26.5
Pallor	16	32.7
Palpable GB	16	32.7
Fever	9	18.4
Ascites	14	28.6

2. Diagnosis of the GBC

GBC is diagnosed pre-operatively at 80% with CT-Scan been over half at 53%, followed by Ultrasound scan at 34.7% and lastly by MRI at 22.4%. A mere 20% of the patients are diagnosed intra-operatively.

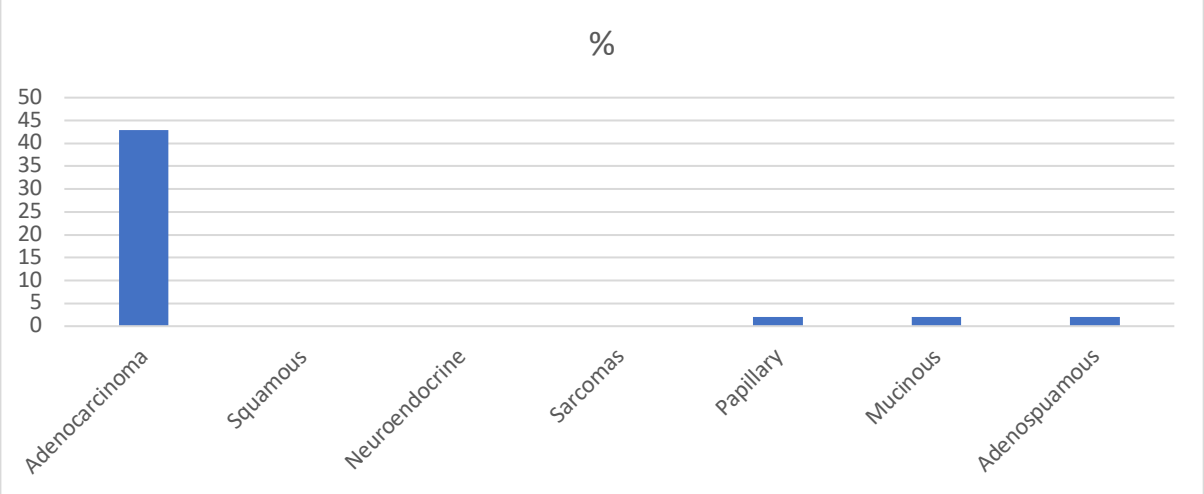
Bar chat 1:Diagnosis



3. Type of GBC

Adenocarcinoma is the commonest type of the malignancy at 88%. Papillary was at 4.2%, mucinous(4.2%) and adenosquamous (4.2%)

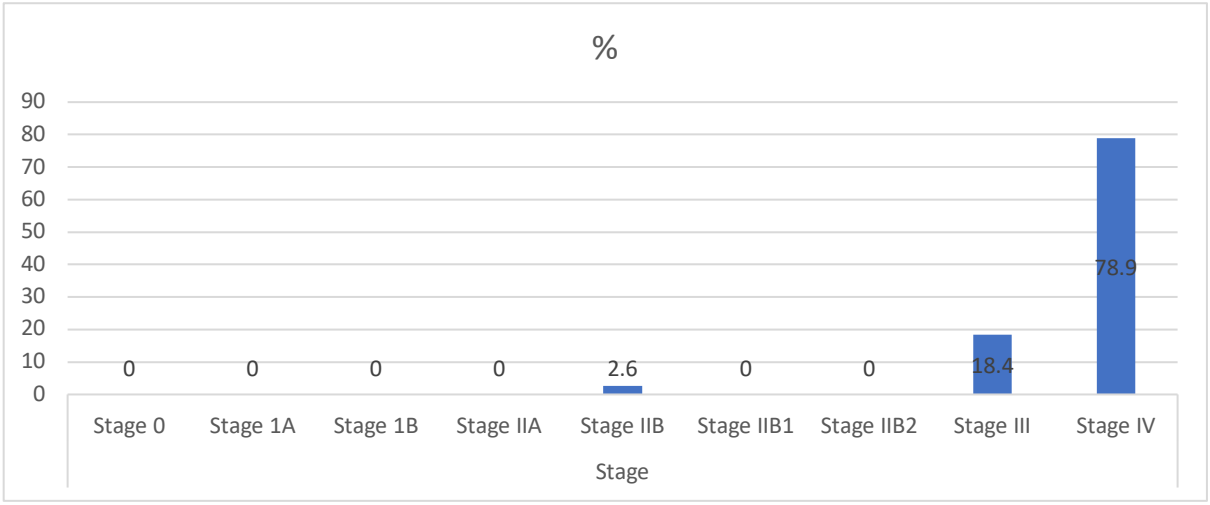
Bar chat 2:Type of GBC



4. Staging of GBC

Stage IV was 78.9% of the patients, stage III was 18.4% and stage II was 2.6% of the patients. The stage IV patients died more at (46.67 %) than the other stages. Those with stage IV malignancy had a 12% higher death rate than those who had other staging of the malignancy.

Bar chat 3:Staging of GBC



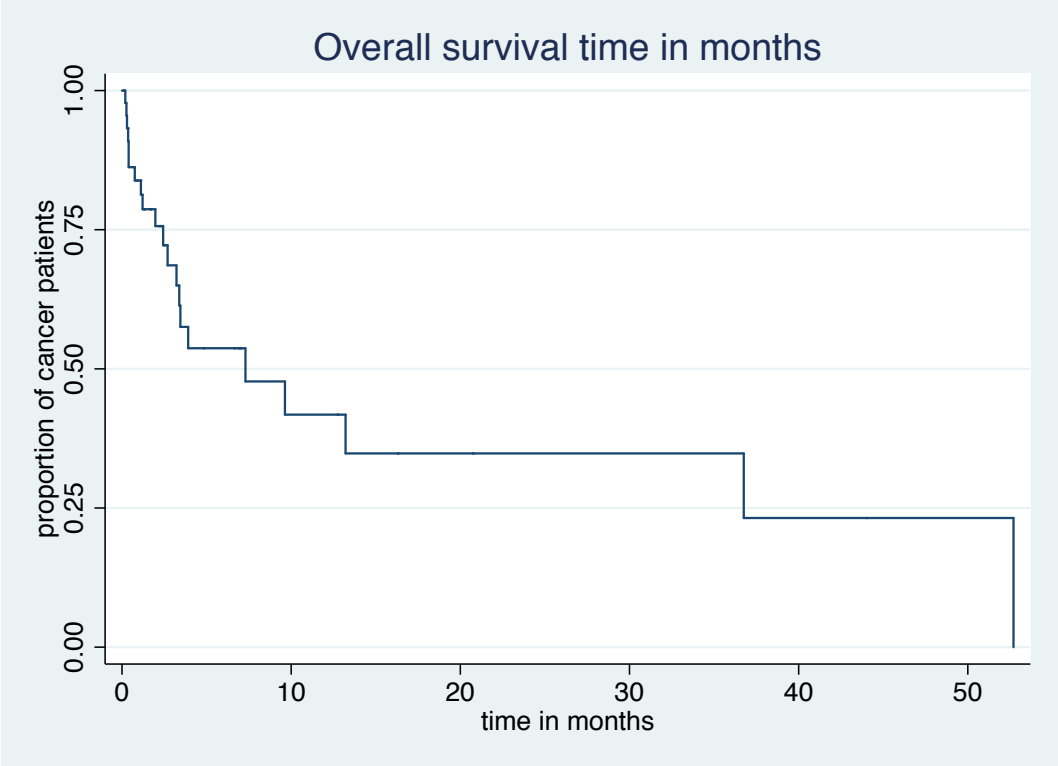
5. Treatment of GBC

44.9% underwent surgery and 20.4% were given chemotherapy where as 10.2% underwent both chemotherapy and surgery. A significant number of patients 24.5% of the patients did not undergo any form of treatment.

6. The survival curves and analysis

The median survival time for most of the patients lived is 7.29 months with an interquartile of 2.4 to 36.75 months. The last observed exit or death was at 52.7 months.

Figure 1:Overall survival time in months



Those above 50 years of age are dying early and also living longer than the patients less than 50 years of age.

On comparing the incidence of death among the females and males, although there were more deaths among female(48.15) participants than among males (40.91), the difference was not statistically significant.When comparing the incidence of death with age of those less than 50 years (54.55) died more than and those above 50 years(42.11).

Figure 2:Kaplan-Meier curve comparing survival by age

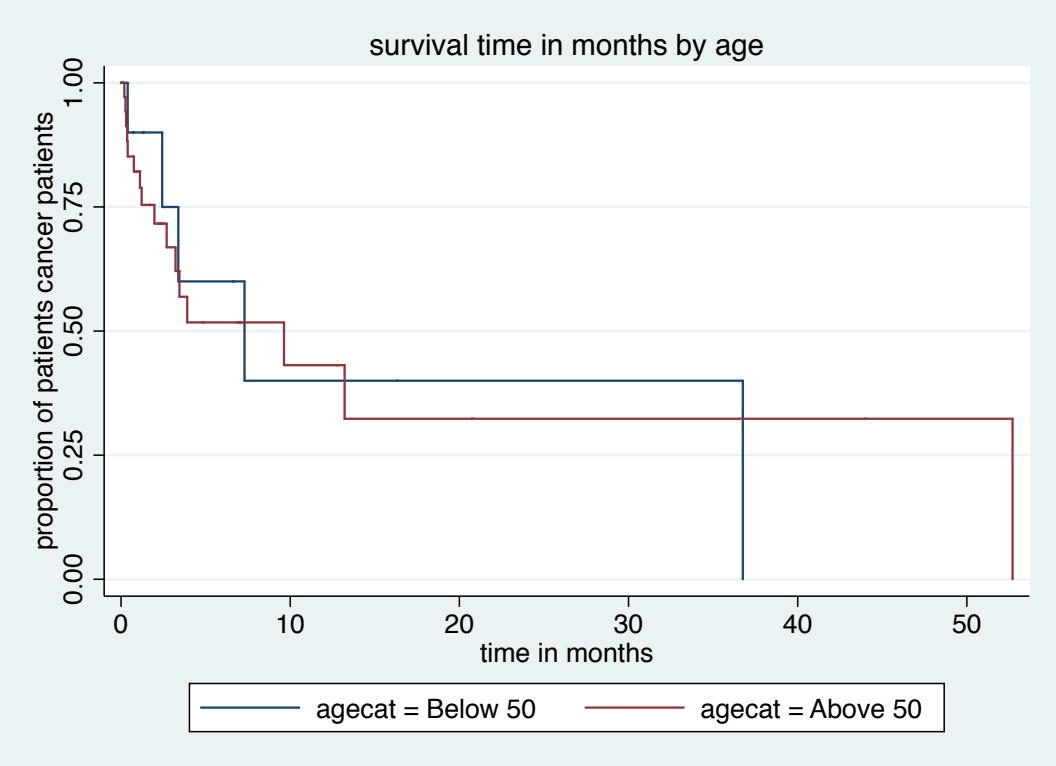


Figure 3:Kaplan-Meier curve comparing stage IV and other stages of cancer

The participants with advanced malignancy died earlier particularly within the first few months. Over time the advanced stage and those without it over time crossed each other.

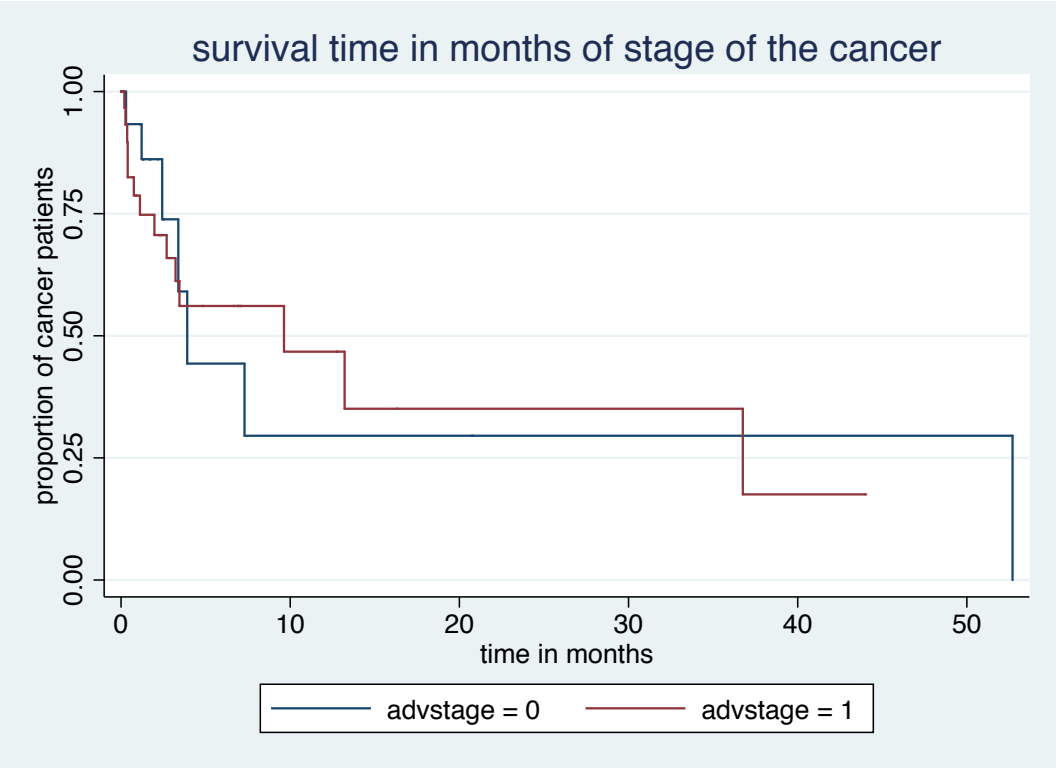
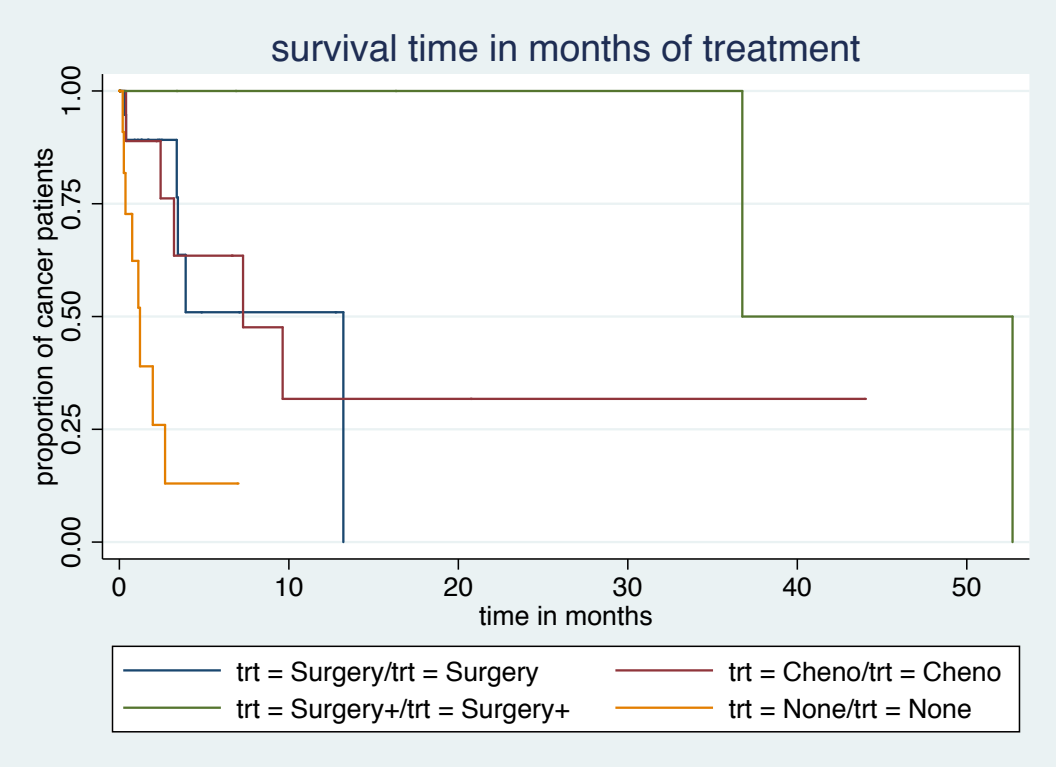


Figure 4:Kaplan-Meier curve comparing treatments

Those who received a combined form of management of surgery and chemotherapy survived longer. Whereas those who did not receive any form of management died earlier.



Cox regression analysis

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]
agecat	1.168092	.6177488	0.29	0.769	.4143018 - 3.293347
n2gender	.7563619	.3517647	-0.60	0.548	.3039887 - 1.881923
preoper	.903811	.2781938	-0.33	0.742	.4943984 - 1.652259
treatment	1.480846	.3127088	1.86	0.063	.9789547 - 2.240048
advstage	1.123076	.55097	0.24	0.813	.4293566 - 2.937651
type	1.242292	.3944732	0.68	0.494	.6667089 - 2.314789

CHAPTER FIVE

8 DISCUSSION

The results of this study have established that GBC is quite fatal as the average survival is less than an year at 7.29 months post diagnosis. The incidence rate of death among these patients was 7% in a month. This means that in a hundred GBC patients in a month 7 of the patients will die. Nevertheless, the longest survival was 52.7 months after the diagnosis mainly for patients who underwent surgery and chemotherapy, thus indicating that if the malignancy is diagnosed early enough a combination of surgery and chemotherapy can prolong the patient's life.

Based on the predictor variables that we investigated, there does not seem to be any that is associated with death from GBC. However, we suspect that with higher sample size, there may be a statistical difference in death rates across gender with females having more deaths than the males. In addition, we also suspect that death may be higher in younger persons and those with advanced stage of the GBC disease. However, this requires further studies to confirm this theory. There is also late diagnosis meaning that the disease will have progressed to advanced stages by the time it is diagnosed resulting in diminished probability for recovery. In our setting most of the diagnosis is being made preoperatively when patients already have many symptoms and hence the disease is diagnosed late unlike in other settings where the diagnosis is made intra-operatively. We don't see any patients being diagnosed in the earlier stages of the disease unlike in other studies. This is in line with findings from other studies which indicate that delayed diagnosis increases the risk of death.

Adenocarcinoma is the most common form of cancer in this GBC population. It is unclear why this is the case. In this regard, it would be worthwhile to conduct a study to determine why this form of cancer is more common. Most of the patients diagnosed are in the 5th decade, suggesting that diagnosis is made when they are susceptible to other non-communicable diseases. This means that there needs to be intensive programs to initiate diagnosis in earlier ages to enhance the chances of treatment and prolonged life.

Further, patients with advanced stage (stage 4) of the malignancy have a 12% more chance of dying than those with the other staging. The advanced stage patients recorded higher deaths, and this could be due to the distant metastasis that was already present and the malignancy may not have been operable causing the patients to undergo chemotherapy or

palliative care. However, there was no statistical significance on the association with death p-value (0.813). Surgery was not curative as majority of the patients were discovered in advanced stages. Of importance to note is that a significant number (24.5%) did not undergo any form of treatment. These are patients who may have died before the start of the treatment or lack of follow through after diagnosis.

9 CONCLUSION

This study has established that the association was not statistically significant between the patients age, gender, type of malignancy, the staging, treatment in Kenya and time to death. Nevertheless, late diagnosis of GBC leads to finding the malignancy at an advanced stage hence curative surgery is not possible. Consequently, the patients who underwent surgery and chemotherapy management had a longer survival.

10 RECOMMENDATIONS

There is need for prospective studies to be conducted on this malignancy to follow up the patients for the entire duration of time to understand more on these factors. There is also a need to have a database which captures all the details on patients diagnosed with GBC from time of diagnosis and end result of the patients.

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