Clinical presentation of complicated gallbladder disease in HIV positive patients at Chris Hani Baragwanath Academic Hospital

Sechaba Thabo Palweni

A research report submitted to the faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Masters of Medicine in the branch of General Surgery

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Declaration

I, Sechaba Thabo Palweni, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of General Surgery at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

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13 March 2020

Johannesburg

Abstract

Background: Symptomatic gallbladder disease is a common surgical condition that requires admission and surgical intervention. In South Africa it is estimated that 7.06 million people are living with HIV/AIDS and it is probable that some of these patients have symptomatic gallbladder disease.

Aim: To explore the demographics, clinical course and progression of symptomatic gallbladder disease in HIV/AIDS patients at Chris Hani Baragwanath Academic Hospital (CHBAH).

Methods: A retrospective analysis of prospectively collected data of patients with confirmed symptoms and signs of symptomatic gallbladder disease namely acute cholecystitis. Patients over 18 years who consent to an HIV test, with the established clinical problem of acute cholecystitis were recruited from the surgical admission wards at CHBAH. Patients with choledocholithiasis, biliary pancreatitis and malignancy were excluded. Demographic data was recorded and the progression of the disease tracked. Patients were recruited over a period between 2013 and 2016, a total of 79 patients were enrolled but only 34 patients were eligible for analysis. The data was analysed with Strata using descriptive statistics.

Results: The age of presentation for symptomatic gallbladder disease was between 30-50 years. 8 of these patients were HIV positive. The treatment received in the cohort was both open cholecystectomy (n=2 HIV negative vs. n=1 HIV positive) and laparoscopic cholecystectomy (n=14 HIV negative vs. n=2 in HIV positive). 1 patient who was HIV positive had acute suppurative cholecystitis. 2 of the patients had postoperative complications. None of the variables used to predict complication of symptomatic gallbladder disease examined in this study were found to be statistically significant.

Conclusion: This study did not conclusively show that patients with HIV/AIDS and symptomatic gallbladder disease have higher rates of postoperative complications. This supports the literature, which suggests that the HIV status of patients should not preclude surgery.

Acknowledgements

I would like to acknowledge my family for their unwavering support and words of encouragement when times were tough.

My supervisors, Prof Smith and Prof Candy, who have provided support, an understanding and without whom I would not have been able to complete my research.

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To the staff of Chris Hani Baragwanath Academic Hospital, I wish to express my heartfelt gratitude for allowing me to conduct my research at the institution.

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Abbreviations

AC	Acute cholecystitis
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline phosphatase
ART	Antiretroviral therapy
BMI	Body Mass Index
CHBAH	Chris Hani Baragwanath Academic Hospital
CRP	C-reactive protein
GGT	Gamma glutamyl transferase
HIV	Human Immunodeficiency Virus
LC	Laparoscopic cholecystectomy
OC	Open cholecystectomy
VL	Viral Load

Section 1: Literature review

1.1 Introduction

Symptomatic gallstone disease is one of the common reasons for surgical admission. Approximately 20 million people in the United States of America have gallstones and the majority of these patients have asymptomatic disease (1). Symptomatic gallstones can be caused by a spectrum of diseases including acute cholecystitis, choledocholithiasis and biliary pancreatitis. Symptomatic disease is often preceded by episodes of biliary colic.

Biliary colic is defined as one or more episodes of upper abdominal pain lasting for at least 30 minutes but less than 6 hours (4) and develops in 1 - 4 % of individuals with gallstone disease annually (1, 5). If left untreated, 20% of these individuals will develop acute cholecystitis (1, 5). Various factors are used to predict the risk of developing symptoms in an individual with gallstones and the likelihood progression from biliary colic to other complications of gallstone disease such as cholecystitis (1,4)

The prevalence of gallstone disease is higher in middle-aged females and the elderly (3, 5). Although females are at higher risk of developing symptomatic gallstone disease, males are more likely to present with complicated disease. Age has also been identified as a risk factor for developing symptomatic gallstone disease, and coupled female gender increases the risk of developing symptomatic gallbladder disease (3). The symptomatic gallstone is also associated with certain comorbidities for example diabetes mellitus, organ transplant patients; patients who have had bariatric surgery

and patients post major surgery. The symptom complex of the disease is dependent on the size of gallstones.

There are three types of gallstones, cholesterol, pigment and mixed types stones. Cholesterol stones tend to be larger and pigment stones, which are predominantly related to hemolytic conditions, tend to be smaller (13). Stones causing acute cholecystitis are often larger than those associated with gallstone pancreatitis.

At Chris Hani Baragwanath Academic Hospital (CHABH), we are at the epicenter of HIV/AIDS epidemic with a prevalence of 22,4% (6, 7). Between 20 - 25 % of these patients will require elective or emergency surgery, sometimes as a result of HIV related disease or incidental pathology unrelated to HIV infection (6). In one cohort study, it was found that postoperative complications were higher in those patients who were HIV positive and especially if they had an emergency procedure. Of the patients with HIV infection, 50 - 79% were malnourished, which may have an effect on the rate of complications (8). Viral load was found to be a better predictor of clinical progression to AIDS and death than CD4 lymphocyte count (9). Two studies showed that there was no difference in the complication rate in those patients with HIV infection and their non-infected counterparts. Therefore the presence of HIV should not affect the surgical management of patients (5). Of the 5,3 million individuals who are HIV positive, the majority are females (5). It is probable that some of these HIV positive patients have gallstone disease. There is insufficient literature on the predominant type of gallstone disease in patients who are HIV positive. It is not known whether HIV and AIDS are risk factors for development of symptomatic gallbladder disease and its complications. Furthermore, whether anti-retroviral treatment modifies the risk has not been studied.

The confirmation of complications is based clinical signs, biochemistry as well as imaging and various guidelines are used to influence management. Some centers follow Tokyo guidelines in management of acute cholecystitis. There is a scarcity of literature on clinical, biochemical and radiological findings in HIV and AIDS patients with complicated gallstone disease. Furthermore the researcher is also not aware of any guidelines specific for management of complicated gallstone disease in HIV and AIDS patients. While practicing, the researcher has seen that some management guidelines and risk scoring systems are applied to patients who are HIV positive and those with AIDS admitted with complicated gallstone disease. It is assumed that they would have the same disease progression and response to treatments their HIV negative counterparts (6,8).

Complications of symptomatic gallstone disease are directly linked to the pathogenesis of each of the disease entities. The cause of acute cholecystitis in patients with calculous disease is that the stone fails to disimpact timeously which results in further inflammation. The disease may progress to develop a mucocele becomes secondarily infected and creates an empyema or an emphysematous gallbladder or can even progress to perforation with peri-cholecystic abscess or generalised peritonitis (1). The main determinant of the above is the duration of impaction and thus without timeous medical intervention, complications may occur.

There are two other complications of gallstones disease with significant morbidity and mortality namely gallstone pancreatitis and obstructive jaundice which may complicate with cholangitis (1,4). The severity of acute pancreatitis varies and a number of systems based on clinical, biochemical and /or radiologic imaging are used

for prognostication (14). In cholangitis the presence of organ dysfunction such as renal failure, septic shock or low Glasgow coma scale would suggest severe disease. However for the purpose of the study, complications such as biliary pancreatitis and choledocholithiasis would not be included.

The definitive treatment of symptomatic gallstones is cholecystectomy, which can be open or laparoscopic. Laparoscopic cholecystectomy is preferred over open cholecystectomy as it is associated with shorter hospital stay, less pain and early return to function (1). Early cholecystectomy is preferred to a delayed cholecystectomy if the patient presents early as the risk of presenting with further attacks of cholecystitis while waiting for surgery is removed and there is a shorter hospital stay. In severe acute cholecystitis, a percutaneous cholecystostomy is preferred in patients who are not fit for surgery. Cholecystostomy is done as a temporizing measure in the acute phase and allows for delayed laparoscopic cholecystectomy (4). HIV and AIDS patients often have multiple other cofounding factors. There is a paucity of information on the safety of same admission laparoscopic cholecystectomy and the rate of conversion from laparoscopic to open cholecystectomy in the acute setting in HIV and AIDS patients operated on for complicated gallstone disease.

If patients require a cholecystectomy for symptomatic gallbladder disease, it is required that the removed gallbladder be sent for histological examination. Classical macroscopic findings in patients with acute cholecystitis are a thickened gallbladder wall with tense, inflamed tissue. If there is subserosal haemorrhage the gallbladder may become red or black. In chronic cholecystitis the gallbladder may be shrunken

and show no inflammatory changes (13). In one study in patients with AIDS the histological examination of the gallbladders showed co-infection with Cryptosporidium, Cytomegalovius (CMV) and mycobacterium avian complex and some cases of Kaposi sarcoma (12). Therefore, the researcher would like to investigate the presentation of symptomatic gallstone disease in HIV and AIDS patients presenting to Chris Hani Baragwanath Academic Hospital. Primary aim is to determine if HIV positive patients have a higher rate of complicated gallbladder disease compared to HIV negative patients. Secondary aim is to determine clinical course of symptomatic gallbladder disease. The choice of surgical intervention in HIV positive patients. Review of final histological examination of gallbladder in patient who had cholecystectomy. Antiretroviral disease has any effect on the clinical outcome in patients with symptomatic gallbladder disease

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Section 2: Author's guidelines

The formatting of this Research Report complies with the University of Witwatersrand style guide for Thesis, Dissertation and Research Reports. The formatting of the draft article may differ from the rest of the Research Report in order to comply with the author guidelines for the journal to which it is intended to be submitted.

In this section the author guidelines that the researcher followed with regard to formatting the article are included and followed by the draft article. The journal to which this article is intended to be submitted is Wits Journal of Clinical Medicine.

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All submission should follow the style of the Journal and clear and concise. The word count should not exceed 5000 words. Email to: Hilda.Potgieter@wits.ac.za

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Structure

The **abstract** (250 words) should outline the main purpose of the study, key methods, the main results and conclusion.

The **Introduction** provides the background to the study and should be sufficient to permit non-specialist to understand the framework of the work. Include well-defined statement regarding the purpose of the study.

The methods: provide a description of the study design, all procedures, techniques and statistical analyses.

The results: stipulate the study findings and ensure to cross-reference figures and tables.

The discussion should elicit an interpretation of the study set against the background of current knowledge of the field and provide definitive conclusions.

Section 3: Draft article

Clinical presentation of complicated gallbladder disease in HIV positive patients at Chris Hani Baragwanath Academic Hospital

Palweni Sechaba*, Smith Martin, Candy Geoffrey

Department of General Surgery, School of Clinical Medicine, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa

Corresponding author

Sechaba Palweni

Department of General Surgery

26 Chris Hani Road

Diepkloof

Johannesburg, 1864

011 933 9267

0826013486

stpalweni@yahoo.com

Smith Martin

Martin.smith@wits.ac.za

Candy Geoffrey

Geoffrey.candy@wits.ac.za

Key words

Gallbladder disease, acute calculous cholecystitis, Human immunodeficiency Virus, Acquired Immunodeficiency Syndrome.

Abstract

Background: Symptomatic gallbladder disease is a common surgical condition that requires admission and surgical intervention. The 7.06 million people that are living with HIV/AIDS some are at risk of developing symptomatic gallbladder disease.

Aim: To explore the demographics, clinical course and progression of symptomatic gallbladder disease in HIV/AIDS patients at Chris Hani Baragwanath Academic Hospital (CHBAH).

Methods: A retrospective analysis of prospectively collected data of patients with confirmed symptoms and signs of symptomatic calculous gallbladder disease namely acute cholecystitis. Patients over 18 years who consent to an HIV test, with the established clinical problem of acute cholecystitis were recruited from the surgical admission wards at CHBAH. Patients with choledocholithiasis, biliary pancreatitis and malignancy were excluded. Demographic data were recorded, and the progression of the disease tracked. Patients were recruited over a period between 2013 and 2016, a total of 79 patients were enrolled but only 34 patients were eligible for analysis. The data was analysed with Strata using descriptive statistics.

Results: The age of presentation for symptomatic gallbladder disease was between 30-50 years. 8 of these patients were HIV positive. The treatment received in the cohort was both open cholecystectomy (n=2 HIV negative vs. n=1 HIV positive) and laparoscopic cholecystectomy (n=14 HIV negative vs. n=2 in HIV positive). 1 patient who was HIV positive had localised complication of acute suppurative cholecystitis. 2 of the patients had postoperative complications. None of the variables used to predict complication of symptomatic gallbladder disease examined in this study were found to be statistically significant.

Conclusion: This study did not conclusively show that patients with HIV/AIDS and symptomatic gallbladder disease have higher rates of postoperative complications. This supports the literature, which suggests that the HIV status of patients should not preclude surgery.

Introduction

Symptomatic gallstone disease is one of the commonest reasons for surgical admission. Approximately 20 million people in the United States of America have gallstones and majority of these patients have asymptomatic disease (1-3). Symptomatic gallstones can clinically present as acute cholecystitis, choledocholithiasis and biliary pancreatitis. Biliary colic may precede complicated gallstone disease.

Biliary colic is defined as one or more episodes of upper abdominal pain lasting at least 30 minutes but less than 6 hours (4) and develops in 1 to 4% of individuals with gallstone disease annually (3). If left untreated, 20% of these individuals will develop acute cholecystitis (1, 3, 5). Various factors are used to predict the risk of developing symptoms in an individual with gallstones and the likelihood of progression from biliary colic to other complications of gallstone disease such as acute cholecystitis (1, 3, 6).

The prevalence of gallstone disease is higher in middle aged females and the elderly (4),(5). Although females are at higher risk of developing symptomatic gallstone disease, males are more likely to present with complicated disease (7, 8). Symptomatic gallbladder disease is also associated with certain comorbidities for example diabetes mellitus, patients who have had bariatric surgery and organ transplantation. The symptom complex of the disease is dependent on the size of the gallstones. There are three types of gallstones namely cholesterol, pigmented and mixed type of stones (9, 10). Cholesterol stones are often larger than pigmented

stones. Pigment stones are predominantly related to haemolytic conditions." Stones causing acute cholecystitis are often larger than those causing biliary pancreatitis.

Currently in South Africa, there are 7.06 million people living with HIV/AIDS and the prevalence rate is approximately 12.6% (11). Chris Hani Baragwanath Academic Hospital (CHBAH) is at the epicenter of HIV/AIDS epidemic due to its location in Gauteng province, the most populated province in the country. It is probable that some of these patients will have symptomatic gallbladder disease. It is estimated that approximately 20 to 25 % of patients with AIDS in their lifetime, will require elective or emergency surgery for pathology related to complications of opportunistic infection or due to surgical pathology unrelated to their HIV status for an example acute cholecystitis (5, 12). Earlier reports placed their post-operative complications rate as high as 20%. However, a study by Leiva, which is the largest study to date on symptomatic gallbladder disease and AIDS reported peri-operative morbidity of less than 5% and mortality rate of 4% (13).

A cohort study by Albaran et al found that complications were higher in HIV positive patients especially if they required emergency procedures (14). In 2 reviews, one by Babamento et al and a second by Madiba et al, the rate of postoperative complications could be influenced by the presence of HIV with a poor nutritional status (5, 15) or patients with CD4 counts less than 200 cells/ug (14). Conversely, three studies showed that there was no difference in the complication rates in those with HIV infection and their negative counterparts. Therefore, the HIV status should not affect their surgical management (5, 16, 17). There is no recent literature describing the type of gallstones that occur in HIV positive patients. It is not known whether HIV/AIDS

places patients at an increased risk for developing symptomatic gallbladder disease or complications. Furthermore, the role of anti-retroviral treatment in modifying the rate of complications of gallstone disease (all types of presentations) has not been studied.

Complications of symptomatic gallbladder disease are directly linked to stones causing an obstruction either in the cystic duct or in the common bile duct. In most patients with acute cholecystitis, the stone causing obstruction at the gallbladder outlet fails to disimpact. The consequences of this include, the formation of a mucocele, an empyema, or an emphysematous gallbladder and can lead to gangrene and perforation of the gallbladder with peri cholecystic abscess or generalised peritonitis (2, 3, 18, 19). The severity of complications is related to the duration of stone impaction and therefore timeous medical intervention is important.

There are two other complications of gallstone disease, which may have significant morbidity and mortality; namely biliary pancreatitis and obstructive jaundice due to stones in the common bile duct and cholangitis (obstructed biliary system with infection) (2, 3, 18). The severity of acute pancreatitis varies, and many systems based on clinical, biochemical and or radiological imaging are used for stratification (18). Severe cholangitis is characterised by presence of organ dysfunction. (18). For the purposes of this study, complications such as biliary pancreatitis and obstructive jaundice due to choledocholithiasis are not included.

The confirmation of complicated gallbladder disease is based on clinical signs; biochemistry as well as imaging and various guidelines are used to influence management. Some centers use Tokyo guidelines in the management of acute

cholecystitis (18). There is a scarcity of literature on clinical, biochemical and radiological findings in HIV and AIDS patients. Studies have shown that HIV positive patients who present with symptomatic gallbladder disease have similar clinical presentation, disease progression and should have the same response to treatment when compared to their HIV negative counterparts (5, 16, 17).

The definitive treatment for symptomatic gallbladder disease is cholecystectomy, which can be performed by open or laparoscopic techniques. Laparoscopic cholecystectomy is the current standard of care and should be performed early (<7-10 days), during the same admission, if patients present early (20-23). Cholecystostomy is performed in patients who are high risk for surgery. It is an accepted temporizing measure in the acute phase and allows for interval or delayed cholecystectomy (24, 25). HIV/AIDS patients often have numerous other comorbidities. There is a paucity of information on the safety of same admission laparoscopic cholecystectomy and the rate of conversion from laparoscopic to open cholecystectomy in acute setting in HIV/AIDS patients who are being operated for complicated gallbladder disease.

It is mandatory that all gallbladders that are removed at cholecystectomy be sent for histological examination. Classical macroscopic findings in patients with acute cholecystitis are an enlarged, tense, inflamed gallbladder and it may assume a red to black appearance due to subserosal haemorrhage (2, 26). In chronic cholecystitis the gallbladder may be shrunken and show no inflammatory changes (26). In HIV/AIDS patients histological examination demonstrated co-infection with Cryptosporidium, Cytomegalovirus and mycobacterium avium complex and some cases of Kaposi Sarcoma (13, 27). Therefore, the researcher would like to investigate symptomatic

gallbladder disease in HIV/AIDS patients presenting to Chris Hani Baragwanath Academic Hospital. The primary aim of the study is to determine if HIV positive patients have a higher rate of complicated gallbladder disease compared to HIV negative patients. The secondary aims are to determine the clinical course of symptomatic gallbladder disease and the choice of surgical intervention in HIV positive patients who present with symptomatic gallbladder disease. The study also aims to review the final histological examination of the gallbladder in patients who had cholecystectomy and explore if antiretroviral disease has any effect on the clinical outcome in patients with symptomatic gallbladder disease (28).

Methods

Permission to conduct the study was granted by the University of Witwatersrand Human Research Ethics Committee in conjunction with the Chris Hani Baragwanath Academic Hospital medical advisory committee. The sample population was recruited from patients that were admitted to the general surgery wards, either electively or as an emergency with a confirmed history of acute cholecystitis. These patients would have complained of abdominal pains located on the right side. On examination pain would be localised to right upper quadrant of the abdomen, and blood tests would show signs of inflammation demonstrated by a raised white cell count and C-reactive protein. On ultrasound there would be evidence of a thickened gallbladder with gallstones, fluid around the gallbladder and sonographic Murphy's sign. In order to be included in the study patients had to be 18 years or older and agree to being tested for HIV after being counseled. If patients were found to be HIV positive, then they would be referred for posttest counseling and initiation of anti-retroviral therapy. Patients

who declined to be tested for HIV, presenting with obstructive jaundice due to gallstones, biliary pancreatitis, and biliary malignancy were excluded from the study.

Descriptive statistics

This is a retrospective review of prospectively collected data. For categorical data, the distribution in numbers and percentages stratified by HIV status was displayed, while for the continuous variables, mean, standard deviation and median with interquartile ranges were computed for both HIV negative and positive patients. To assess the association between various factors and HIV positive status, Pearson chi-squared test and fisher's exact test was used. Test of proportionality was also used to assess difference in proportion for HIV positive by Anti-retroviral categories. Two sample student t-test was employed to assess the average distribution of continuous variables according to HIV status, also a Wilcoxon sign rank test for non-nominally distributed data was used to assess median differences.

Results

A total of 79 patients were recruited from a period of 01 January 2013 to 31 December 2016, (see Figure 1). Only 34 patients were eligible for analysis. The distribution of patient's demographic data (see Table 1) reflects that there were 26 HIV negative and 8 HIV positive patients. There were 33 females and only 1 male included in the study. The median age distribution between HIV negative and positive patients was similar; 39 years for HIV positive and 43 years HIV negative patients respectively (p=0.45). 3 (37.5%) patients between the ages of 20-29 and 3 (37.5%) patients over the age of 50 who were HIV positive, presented with acute cholecystitis as compared to 5 (19.2%) patients between the ages 20 – 29 and 8 (30.8%) patients

over the age of 50 who were HIV negative. None of the variables were statistically significant.

The sample group is highlighted in Table 2. There was found to be no association between symptoms and HIV status. A larger number of HIV negative patients 25 (96.15%) presented with abdominal pain than HIV positive patients 7 (87.50%). Furthermore of those patients with abdominal pain more HIV negative patients, 11 (42.3%) had pain for more than 72 hours as compared to HIV positive patients 3 (37.5%). Nausea was prevalent in both groups; a higher number of HIV positive patients 7 (87,5%) than HIV negative patients 21 (80,77%) presented with this symptom and 62.5 % HIV positive patients as opposed to 50% HIV negative patients reported vomiting. Most of the patients, both HIV positive (n = 5) and negative (n = 9), were presenting for the first time with symptoms of gallbladder disease. The majority of patients were obese with a BMI between 30 and 34.9 (according to the WHO classification). Additionally a greater number of HIV negative patients 16 (61.54%) were obese, in contrast to 4 (50%) of the HIV positive patients. None of the patients recruited in the study were malnourished, that is BMI less than 18.5 kg/m^2. None of these findings were statistically significant.

Table 3 describes the distribution of HIV positive patients by anti-retroviral (ART) medication. The percentage distribution of HIV positive patients on ART and not ART was equal in both groups. The median CD4 count in the ART naïve was 430 and those on ART was 285. This was not statistically significant (p=0.72). The difference in viral load in both groups was not significant.

Table 4 shows the range of surgical interventions performed on the sample group. The majority of patients were first time admissions, treated non-operatively and planned for delayed cholecystectomy. Three patients who presented as emergencies were subjected to open cholecystectomies; two of those were HIV negative and one was HIV positive. The reason for such a low number of patients who had cholecystectomy was the limited institutional resources and logistics. Some of the patients (n = 20) progressed to choledocholithiasis and thus were excluded from the study. At the conclusion of the study there were also patients lost to follow up. There was no statistically significant association between surgical procedures and HIV status. The majority of patients had laparoscopic cholecystectomies; HIV negative 53.85% and HIV positive 25%. Only 2 patients had surgical complications, one was HIV positive and the other HIV negative. The HIV positive patient had a bile leak, which was treated conservatively. The HIV negative patient had a pulmonary embolus that was treated with medical therapy. The reason for the pulmonary embolus was thought to be related to BMI and the fact that the patient was a Type 1 diabetic with target organ damage. In the laparoscopic group there was no difference in terms postoperative length of stay, which was a median of 2 days. However, in the open surgery group the post operative length of stay in HIV negative and HIV positive patients was 10.5 and 21 days respectively. This too was not of clinical significance.

The distribution of clinical biochemistry, histological and non-operative treatment is shown in table 5. The median values for white cell count (WCC), C-Reactive Protein (CRP) and gamma glutamyl transferase (GGT) tests were similar in both groups. For alkaline phosphate (ALP), a higher median result was seen in HIV positive patients 132 (IQR 117-157) than for HIV negative patients 90 (IQR 68-103) which were

statistically significant (p=0.0042). The reason for the raised ALP was not due to gallstones in the common bile duct. This was supported by the results of their magnetic resonance cholangiopancreatography (MRCP), which also showed no stones. A higher number of patients treated with antibiotics were HIV positive, even though no bacteria was cultured or seen on histological examination of gallbladder specimens. Due to logistical reasons, a significant proportion of patients 10 (38%) in the HIV negative group and 5 (62.5%) in the HIV positive group) did not get an early cholecystectomy. These patients settled with antibiotics. It would seem that the HIV patients responded to antibiotics in the majority of cases. Chronic cholecystitis was the main histology type. One patient in the HIV positive group had the localised gallbladder complication of acute supurative cholecystitis, with no evidence of gangrene. In our HIV positive cohort none of the histology showed a secondary cause of acute cholecystitis. Our sample is too small to make definitive conclusions.

Discussion

This study draws parallels with what is described in the literature; there is no difference in outcomes between HIV positive and HIV negative patients with symptomatic gallstone disease. There were no differences in the clinical presentation of the two groups.

The majority of patients presented with abdominal pain, which was mainly right upper quadrant pain. Abdominal pain was present for longer than 72 hours (HIV negative 42% vs. HIV positive 37.5 %). The majority of HIV positive patients were presenting for the first time to the health facility with symptomatic gallbladder disease, (HIV negative 34.62% vs. HIV positive 62.5%).

The clinical suspicion of symptomatic gallbladder disease was confirmed with biochemical and radiological investigation. Of significance in our study was a raised alkaline phosphatase level in HIV positive patients, which could be indicative of presence of stones in the common bile duct. Patients who had persistently raised alkaline phosphatase levels and in whom ultrasonography didn't show stones in the bile duct would then have a magnetic resonance cholangiopancreatography (MRCP), which would confirm that there were no stones in the common bile duct. The reasons for raised alkaline phosphatase could be stones in the common bile duct. Inflammation around the porta hepatis pointing to the severity of acute cholecystitis. (29, 30). Lastly patients who have been on antiretroviral medication for a prolonged period of time may have raised ductal enzymes. Although our study could not demonstrate the latter due because of the study is not powered to draw a firm conclusion (31).

The treatment of mild acute cholecystitis is mainly supportive, implying intravenous fluids and analgesia (32, 33). In this study patients who presented with mild disease and had raised inflammatory markers were placed on empiric antibiotics. This practice is contrary to the Tokyo guidelines 2018 and in the systematic review by A.H van Dijk et al which suggest that antibiotics are indicated as prophylaxis in the perioperative period, an hour before the skin incision is made and there is no need for extended doses of antibiotics (32, 33). Antibiotics are indicated in patients who present with severe acute cholecystitis. The choice of antibiotics is initially broad spectrum and once an organism has been cultured and sensitivity established, treatment is de-escalated. In contrast to this, patients in this study, who had mild to moderate disease were placed on empiric antibiotics and could not be stepped down to targeted treatment as no causative organism was ever identified. Furthermore no routine blood or bile cultures were done. The principles concerning the choice of antibiotics should be guided by antibiotic stewardship and by an instuition's bacteriogram. (34).

Laparoscopic cholecystectomy has been established as the gold standard for symptomatic gallbladder disease and the exact timing of the procedure for the best outcomes remains unanswered (18). The evidence has repeatedly demonstrated that early cholecystectomy (within seven days onset of symptoms) is safe, provided the requisite skills are available to perform the procedure. Data suggests that early cholecystectomy is preferable if logistically possible. Inadvertently, due to logistics, our institution continues to practice a delayed cholecystectomy strategy (35). For HIV positive patients admitted to our institution the procedure of choice is a laparoscopic

cholecystectomy and all gallbladders are submitted for histological examination. With the delayed approach, patients need to be re-admitted for their procedure and some may have recurrent admissions for repeat episodes of acute cholecystitis that may progress to complicated gallbladder disease. The problem with the delayed approach is that patients need to be re-admitted for their procedure. The available data has not demonstrated superiority of one strategy over the other (36, 37).

Although the histological examination of the gallbladders submitted revealed chronic cholecystitis as commonest finding, the small cohort did not reveal a secondary cause of cholecystitis i.e. bacterial, viral or fungal organism. There are however studies that revealed secondary causes of acute cholecystitis(13, 27). There is a growing body of evidence that implies that early initiation of highly active anti-retroviral therapy has lead to an improved immunity, and a reduced number of opportunistic infections with a resultant improvement in operative morbidity and mortality of patients living with HIV/AIDS (38, 39). This could explain why in our study no secondary causes of acute cholecystitis were found.

Limitation and Recommendations

The study was limited by a small sample size and difficulty collecting the proposed number of patients. The number of patients with AIDS was insignificant and therefore one could not conclusively say that the HIV/AIDS patient population is at an increased risk of complicated symptomatic gallbladder disease. The study could have been conducted at a secondary hospital where we could have recruited a larger number of patients and would have operated on them due to better logistics. A lot of patients were lost to follow up and never had their cholecystectomy. This affected our

ability to collect data. We would recommend that patients that present with symptomatic gallbladder disease be operated within 7 days of onset of symptoms, provided the requisite skills to do a safe cholecystectomy are available. Our reported complication rate of 12,5% should be interpreted with caution. Patients with HIV/AIDS should not be denied surgery for symptomatic gallbladder disease.

Conclusion

Our study showed that patients with HIV/AIDS did not have higher rates of complications due to symptomatic gallstone disease. Patients who are immune compromised due to HIV should be managed in a similar way to immune competent patients presenting with acute cholecystitis.

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Tables

Figure 1: Flow diagram of inclusion and exclusion criteria and the number of patients in each category

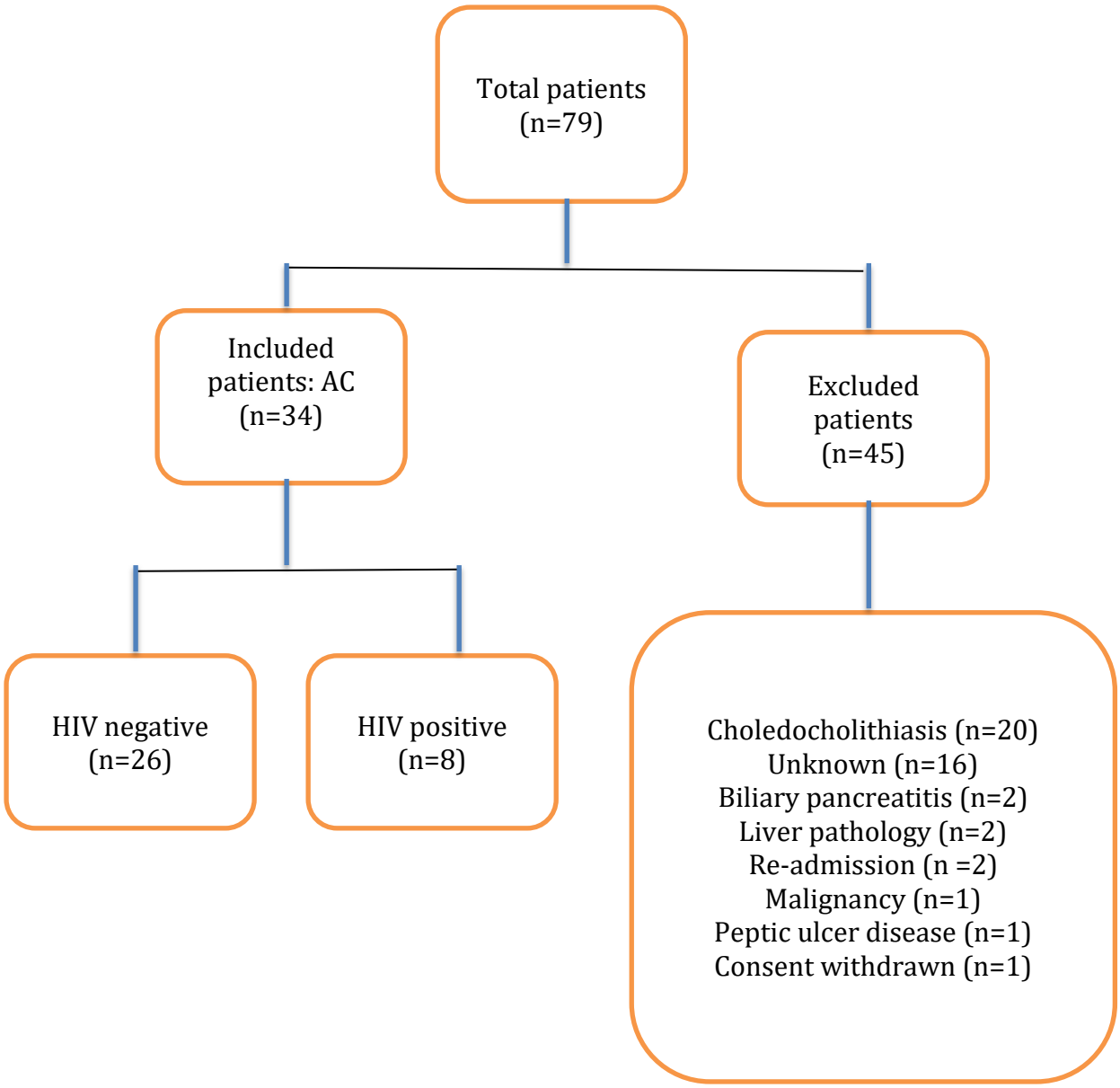


Table 1: Patient demographics

	HIV Negative (n=26)	HIV Positive (n=8)	Total (n=34)	p value
Male	0	1 (12,5%)	1 (3%)	
Female	26 (100%)	7 (87.5%)	33 (97%)	0.23
Mean Age (SD)	43.4 (2.7)	39.1 (5.1)		0.45
Age				
20-29 Years	5 (19.2%)	3 (37.5%)	8 (24%)	
30-50 Years	13 (50.0%)	2 (25.0%)	15 (44%)	
50+ Years	8 (30.8%)	3 (37.5%)	11(32%)	0.40
(0) zero or absent SD = Standard deviation				

Table 2: Clinical presentation of symptomatic gallstone disease

	HIV Negative (n = 26)	HIV Positive (n = 8)	Total (n = 34)	p value
Abdominal pain				
No Pain	1 (3.9%)	1 (12.5%)	2 (6%)	
Pain	25 (96.1%)	7 (87.5%)	32 (94%)	0.42
Duration of symptoms				
<24 hours	1 (3.9%)	1 (12.5%)	2 (6%)	
24-48 hours	7 (26.9%)	1 (12.5%)	8 (24%)	
48-72 hours	7 (26.9%)	3 (37.5%)	10 (29%)	
>72 hours	11 (42.3%)	3 (37.5%)	14 (41%)	0.63
Nausea				
No	5 (19.2%)	1 (12.5%)	6 (18%)	
Yes	21 (80.8%)	7 (80.8%)	28 (82 %)	0.56
Vomiting				
No	13 (50%)	3 (37.5%)	16 (47%)	
Yes	13 (50%)	5 (62.5%)	18 (53%)	0.69
Number of admissions for AC				
1	9 (34.6%)	5 (62.5%)	14 (42%)	
2	8 (30.8%)	1 (12.5%)	9 (26 %)	
3	7 (26.9%)	2 (25%)	9 (26 %)	
4	2 (7.7%)	0	2 (6%)	0.67
BMI (WHO)				
Normal weight (18.5 - 24.9)	6 (23.1%)	3 (37.5%)	9 (26%)	
Overweight (25 - 29.9)	4 (15.4%)	1 (12.5%)	5 (15%)	
Obese (30 - 34.9)	16 (61.5%)	4 (50%)	20 (59%)	0.85
(0): zero or absent, AC = acute cholecystitis				

Table 3: Distribution of HIV positive patients on ART for gallbladder disease

	ART naïve	ART treatment	Total (n=8)	p value
Number of patients	4 (50%)	4 (50%)	8 (100%)	
Median CD4 (IQR)	430 (0 - 611)	285 (120 - 428)		0.72
Median Viral Load (IQR)	0 (0 - 173781)*	12.5 (0 - 25)		0.15
ART: Anti-retroviral therapy, *: 3 missing data.				

Table 4: Description of Diagnostics and Surgical Interventions

	HIV Negative (n=26)	HIV Positive (n=8)	Total (n=34)	P values
Ultrasound				
No	2 (7.69%)	1 (12.5%)	3 (9 %)	
Yes	24 (92.31%)	7 (87.5%)	31 (91%)	0.68
Gastroscopy				
No	21 (80.77%)	7 (87.5%)	28 (82%)	
Yes	5 (19.23%)	1 (12.5%)	6 (18 %)	0.66
Surgical interventions				
No intervention	10 (38.46%)	5 (62.5%)	15 (44 %)	
Laparoscopic cholecystectomy	14 (53.85%)	2 (25.0%)	16 (48 %)	
Open cholecystectomy	2 (7.69%)	0	2 (6 %)	
Open subtotal cholecystectomy	0	1 (12.5%)	1 (2 %)	0.15
Complications				
No	25 (96.15%)	7 (87.5%)	32 (94%)	
Yes	1 (3.85%)	1 (12.5%)	2 (6%)	0.42
Post-operative LOS				
LC IQR (Median)	2 - 2 (2)	2 - 2 (2)		0.80
OC IQR (Median)	7 - 14 (10.5)	21 - 21 (21)		0.22
(0): zero or absent. LOS:Length of stay, LC: Laparoscopic cholecystectomy, OC: Open cholecystectomy				

Table 5: Description of clinical biochemistry, histology and non-operative treatment

	HIV Negative (n=26)	HIV Positive (n= 8)	Total (n=34)	p value
WCC median (IQR)	8.10 (6.56 -11)	5.62 (4.3-9.3)		0.11
CRP median (IQR)	15.4 (5- 19.3)	121.5 (15-306)		0.19
ALP median (IQR)	90 (68-103)	132.5 (117- 157)		0.004
Antibiotics				
No	17 (65.38%)	3 (37.50%)	20 (59%)	
Yes	9 (34.62%)	5 (62.50%)	14 (41%)	0.23
Type of Antibiotics				
Amoxicillin-clavulanic acid	7 (26.92%)	1 (12.50%)	8 (24%)	
Pipercillin-tazobactum	3 (11.54%)	2 (25.00%)	5 (15%)	
Ceftriaxone + Metronidazole	0	1 (12.50%)	1 (3%)	
Amoxil + Metronidazole	1 (3.85%)	0	1 (3%)	
Ciprofloxicillin	0	1 (12.50%)	1 (3%)	0.14
Histology				
No surgical intervention	10 (38.46%)	5 (62.50%	15 (44%)	
Chronic cholecystitis	11 (42.31%)	0	11 (32%)	
Ulcerated cholecystitis	1	1	2 (6 %)	
Moderate active cholecystitis	1	0	1 (3%)	
Acute suppurative cholecystitis	0	1	1 (3%)	
Severe mucosal autolysis	1	0	1 (3%)	
Moderate chronic active cholecystitis	1	0	1 (3%)	
Xantogranulomatous cholecystitis	1	0	1 (3%)	
Eosinophilia	0	1	1 (3%)	0.07
NB: (0) zero or absent. WCC = white cell count, CRP= C-reactive protein and ALP = alkaline phosphatase				

Section 4: Appendices

4.1 Postgraduate approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

05 January 2018
Person No: 1032555
PAG

Dr ST Palweni
P. O Box 3291
Witkoppen EXT 108
2068
South Africa

Dear Dr Palweni

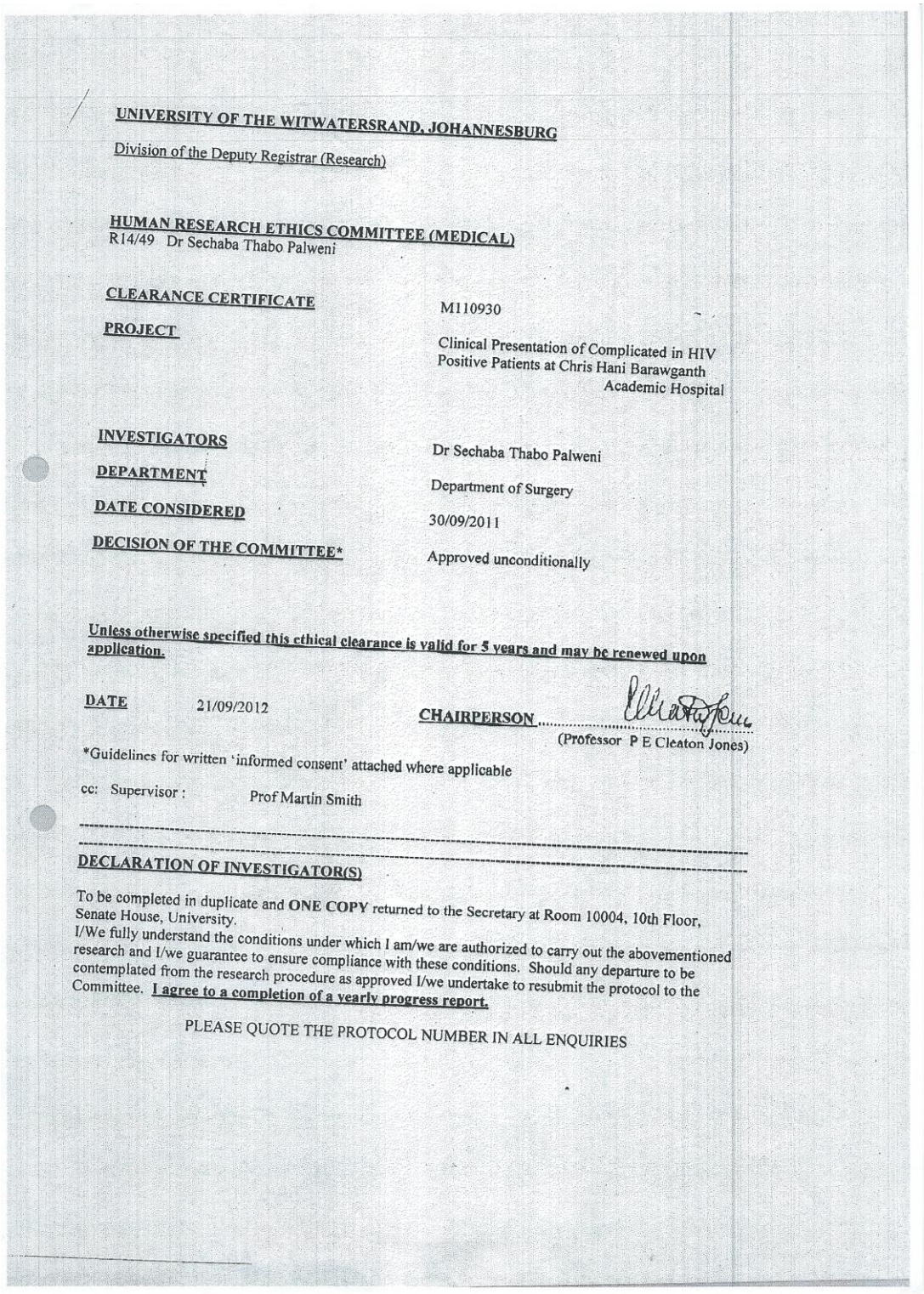
Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Clinical presentation of complicated gallbladder disease in HIV positive patients at Chris Hani Baragwanath Academic Hospital* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

4.2 Ethics approval



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Sechaba Thabo Palweni

CLEARANCE CERTIFICATE	M110930
PROJECT	Clinical Presentation of Complicated in HIV Positive Patients at Chris Hani Barawganth Academic Hospital
INVESTIGATORS	Dr Sechaba Thabo Palweni
DEPARTMENT	Department of Surgery
DATE CONSIDERED	30/09/2011
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 21/09/2012 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

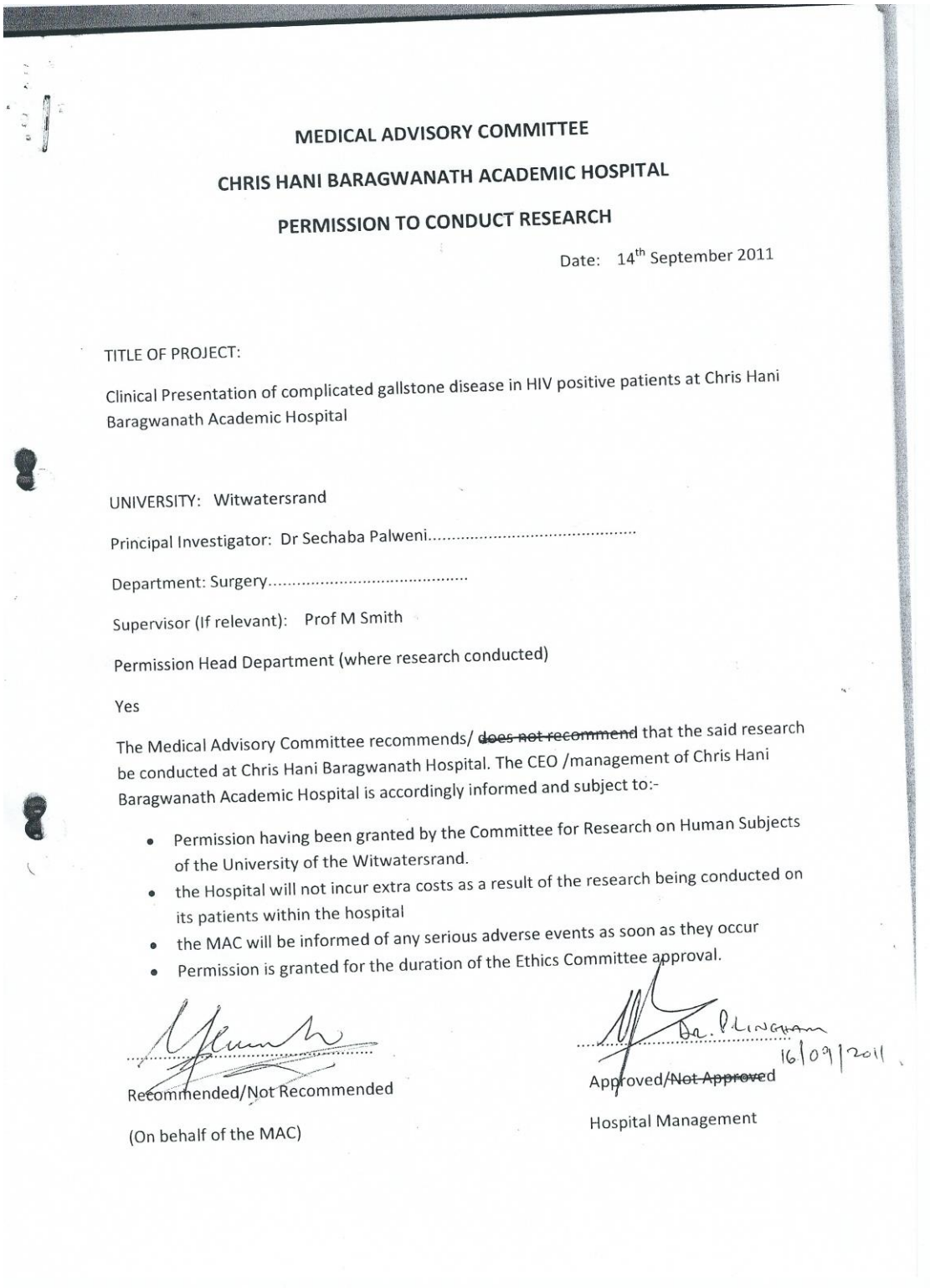
cc: Supervisor : Prof Martin Smith

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

4.3 CEO approval



MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 14th September 2011

TITLE OF PROJECT:

Clinical Presentation of complicated gallstone disease in HIV positive patients at Chris Hani Baragwanath Academic Hospital

UNIVERSITY: Witwatersrand

Principal Investigator: Dr Sechaba Palweni.....

Department: Surgery.....

Supervisor (If relevant): Prof M Smith

Permission Head Department (where research conducted)

Yes

The Medical Advisory Committee recommends/ ~~does not recommend~~ that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Academic Hospital is accordingly informed and subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee approval.

Recommended/Not Recommended

(On behalf of the MAC)

Dr. P Lingham 16/09/2011

Approved/~~Not Approved~~

Hospital Management

4.4 Turn it in report

1032555:MMed_Draft_26_june_2019.docx

ORIGINALITY REPORT

4%	1%	4%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	1%
2	Biliary Lithiasis, 2008. Publication	1%
3	wiredspace.wits.ac.za Internet Source	1%
4	"Gastrointestinal Emergencies", Springer Nature, 2019 Publication	1%
5	"The Management of Gallstone Disease", Springer Nature, 2018 Publication	1%

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		

Section 5: Proposal

Clinical presentation of complicated gallbladder disease in HIV positive patients at Chris Hani Baragwanath Academic Hospital

Sechaba Palweni
Student Number: 1032555
Degree: Master of Medicine in Surgery

Supervisor	Prof. Martin Smith Department of General Surgery
Co-supervisor	Prof. Geoffrey Candy Department of General Surgery

Introduction

Symptomatic gallstone disease is one of the common reasons for surgical admission. Approximately 20 million people in the United States of America have gallstones and the majority of these patients have asymptomatic disease (1). Symptomatic gallstones can be caused by a spectrum of diseases including Acute Cholecystitis, Choledocholithiasis, and Biliary Pancreatitis. Symptomatic disease is often preceded by episodes of biliary colic.

Biliary colic is defined as one or more episodes of upper abdominal pain lasting for at least 30 minutes but less than 6 hours (4) and develops in 1 - 4 % of individuals with gallstone disease annually (1,5). If left untreated, 20% of these individuals will develop acute cholecystitis (1,5). Various factors are used to predict the risk of developing symptoms in an individual with gallstones and the likelihood progression from biliary colic to other complications of gallstone disease such as cholecystitis (1,4)

The prevalence of gallstone disease is higher in the middle aged females and the elderly (3,5). Although females are at higher risk of developing symptomatic gallstone disease, males are more likely to present with complicated disease. Age has also been identified as a risk factor for developing symptomatic gallstone disease, and coupled with female gender increases the risk of developing symptomatic gallbladder disease (3). The symptomatic gallstone is also associated with certain comorbidities for example diabetes mellitus patients, post organ transplant patients, patients who have had bariatric surgery and patients post major surgery. The symptom complex of the disease is dependent on the size of gallstones.

There are three types of gallstones, cholesterol, pigment and the mixed types stones. Cholesterol stones tend to be larger and pigment stones, which are predominantly related to hemolytic conditions, tend to be smaller (13). Stones causing acute cholecystitis are often larger than those associated with gallstone pancreatitis.

At Chris Hani Baragwanath Academic Hospital (CHABH), we are at the epicenter of HIV/AIDS epidemic with a prevalence of 22,4% (6,7). Between 20 - 25 % of these patients will require elective or emergency surgery, sometimes as a result of their HIV related disease or incidental pathology unrelated to HIV infection (6). In one cohort study, it was found that complications were higher in those patients who HIV infection were HIV positive and especially if they were done as emergency procedure. 50 - 79% percentages of patients with HIV infection were malnourished, which may have an effect on the rate of complications (8). Viral load was found to be a better predictor of clinical progression to AIDS and death than CD4 lymphocyte count (9). Two studies showed that there were no difference in the complication rate in those patients with HIV infection and their non-infected counterpart. Therefore should not affect the surgical management of HIV patients (6,7). Of 5,3 million of individuals who are HIV positive, majority are females (6,7). It is probable that some of these HIV positive patients have gallstone disease. Up to now there has not been literature on the predominant type of gallstone disease in patients who are HIV positive. It is not known whether HIV and AIDS are risk factors for development of symptomatic gallbladder disease and its complications. Furthermore, whether anti-retroviral treatment modifies the risk has not been studied.

Complications of symptomatic gallstone disease are directly linked to the pathogenesis of each of the disease entities. Although in the majority of patient with acute cholecystitis, the causative stone causing obstruction at the gallbladder outlet fails to disimpacts, the disease progresses to develop a mucocele, an empyema, an emphysematous gallbladder and perforation with peri-cholecystic abscess or generalised peritonitis (1). The main determinant of the above is the duration of impaction and thus without timeous medical intervention, complications may occur.

There are two other complications of gallstones disease with significant morbidity and mortality namely gallstone pancreatitis and obstructive jaundice which may complicate with cholangitis (1,4). The severity of acute pancreatitis varies and various systems based on clinical, biochemical and /or radiologic imaging are used for prognostication (14). In cholangitis the presence of organ dysfunction such as renal failure, septic shock or low Glasgow coma scale would suggest severe disease. However for the purpose of the study, complications such as biliary pancreatitis and choledocholithiasis would not be included.

The conformation of complicated is based on clinical signs; biochemistry as well as imaging and various guidelines are used to influence management. Some centers follow Tokyo guidelines in management of acute cholecystitis. There is a scarcity of literature on clinical, biochemical and radiological findings in HIV and AIDS patients with complicated gallstone disease. Furthermore the researcher is also not aware of any guidelines specific for management of complicated gallstone disease in HIV and AIDS patients. While practicing, the researcher has seen that some management guidelines and risk scoring systems are applied to patients who are HIV positive and

those with AIDS admitted with complicated gallstone disease. It is assumed that they would have the disease progression and response to treatments their HIV negative counterparts (6,8).

The definitive treatment of symptomatic gallstones is cholecystectomy, which can be open or laparoscopic. Laparoscopic cholecystectomy is preferred nowadays is done during same admission, if patients presents early (1). Cholecystostomy is done in patients who are high risk for surgery and is accepted temporizing measure in the acute phase and allow for interval laparoscopic cholecystectomy (4). HIV and AIDS patients often have multiple other cofounding factors. There is a paucity of information on the safety of same admission laparoscopic cholecystectomy, the rate of conversion from laparoscopic to open cholecystectomy in acute setting in HIV and AIDS patients who being operated for complicated gallstone disease.

It is mandatory that all gallbladders are removed for complicated gallstone disease and sent for histological examination. Classical findings in patients with acute cholecystitis are enlarged gallbladder; it can be tense, inflamed and assume a red to black appearance due to subserosal haemorrhage. In chronic cholecystitis the gallbladder may be shrunken and show no inflammatory changes (13). However studies have showed that in patients HIV/AIDS histological examination showed co-infection with Cryptosporidium, Cytomegalovius (CMV) and mycobacterium avian complex and some cases of Kaposi sarcoma (12). Therefore the researcher would like to investigate presentation of symptomatic gallstone disease in HIV and AIDS patients presenting to Chris Hani Baragwanath Academic Hospital. The type of gallstones, type of complications, findings on examination, response to treatment and

the histological findings post cholecystectomy. The findings would be compared to patients with symptoms of gallstone disease who are HIV negative. Additionally the researcher would like to study how anti-retroviral disease influences the outcome.

Objectives

1. To compare the demographics of patients who are HIV positive with or without AIDS and their HIV negative counterparts presenting with gallbladder disease at CHBAH.
2. To compare disease progression and clinical course of patients who are HIV positive with or without AIDS and their negative counterparts presenting with symptomatic gallbladder disease.
3. To determine if the presentation of complicated gallstone disease in patients who are HIV is influenced by anti-retroviral treatment.
4. To compare the choice of surgical intervention and treatment outcomes of patients who are HIV positive with or without AIDS and their HIV negative counterparts presenting with complicated gallstone disease.
5. To compare the histological findings in gallbladder specimens of patients who are HIV positive with or without AIDS and their HIV negative counterparts who had cholecystectomy for gallbladder disease

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Hypothesis

An HIV positive presents with a higher prevalence of complicated symptomatic gallstones disease.

Study design: Descriptive study, retrospective review of prospectively collected data

Setting: Department of Surgery CHBAH

Sample size: N = 250 patients

Period: August 2011 to December 2016

Population: patients presenting with symptomatic gallstone disease at CHBAH

Inclusion criteria: patients presenting with symptomatic gallbladder disease above age of 18 years old

Exclusion criteria: patients with choledocholithiasis, biliary pancreatitis and malignancies.

Patients who present with biliary pancreatitis, choledocholithiasis or evidence or suspicion of gallbladder malignancy will be excluded.

Data analysis

Mean and range age, percentage HIV positive and percentage on treatment, Chi square, T test, ANNOV, correlation. P-value less than 0.05 will be considered significant.

Ethics

Permission granted by the WITS ethics committee: M110930

Data sheet

Attached

Funding

No additional costs other than stationery

Problems

Patients refusing to do an HIV test. Patients who refuse to participate in the study.

Data Sheet

DATA SHEET

Research number: Age:

Gender: M/F BMI:

Waist circumference: Days of admission:

Symptoms:

abdominal pain(s)	yes	no		
duration (hours)	<24	24-48	48-72	>72
nausea	yes	no		
vomiting	yes	no		
jaundice	yes	no		
presentation	first	second or more		

Investigations:

HIV	*positive*	*negative*
Viral load: CD4:	WCC:	Platelet:
CRP:	HbA1c:	Amylase:
Lipase:	Total billi:	Dir. Billi:
Total protein:	Alb:	ALP:
GGT:	ALT:	AST:

Management:

Antibiotics	*Yes*	*No*

Gastroscopy	*Yes*	*No*			
Ultrasound	*Normal*	*GB*	*Peri-cystic*	*Stones*	*No*
ARVs	*Nil*	*RRTI*	*nRRTI*	*PI*	*Other*
Any other:					

Complications:

Surgery:

Lap chole	
Open chole	
Subtotal	
Cholecystostomy	
ERCP	
Relook	

Bleed	
Biliary leak	
Retained stones	
Sepsis	
Repeat ERCP	
Other:	

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