A glance at gallstones in South Africa:

A one year review of sonographic findings at a tertiary hospital

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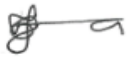
DECLARATION

I, **Dr. Tarisai Sharon Nyahoda** (student number 308224) do hereby declare that this research report is my own work. It is submitted in partial fulfillment of the requirements of the Master of Medicine in Internal Medicine at the University of the Witwatersrand. This report has not been submitted before for any degree or examination at any other university. Where I have used the thoughts or ideas of others, the required referencing conventions have been adhered to.

Signed:



Date : 20 June 2016

DEDICATION

I dedicate this work to my mother Mrs M Nyahoda who has always been there for me, and to my father Mr M.E Nyahoda (RIP) who always encouraged me to give my best in life. I would also like to dedicate this work to my siblings and to thank them for their unwavering support and encouragement

Tarisai Sharon Nyahoda

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ABSTRACT

Background. Gallstones (GS) have historically been thought to be uncommon in Sub-Saharan Africa. There are scanty data on the current prevalence of GS in South Africa despite a significant change in the GS risk factor prevalence.

Objectives. To determine the prevalence and risk factors for GS among adult patients undergoing abdominal ultrasound scans at a tertiary institution.

Methods. We conducted a retrospective cross sectional analysis of all adult abdominal ultrasound scan reports from the radiology department of the institution in the year 2009. Basic demographics, presence, symptoms and complications of gallstones were collected. Logistic regression was used to explore both dependent and independent risk factors for developing GS.

Results. Of the 3 494 reports analysed, 284(8.1%) had GS [95% confidence interval 7.2 - 9.1], with 70% being female. Gallstone prevalence was 10.2% and 5.5% for females and males respectively with a symptomatic to asymptomatic GS ratio of 1:1.9. Complications were seen in 6.3% of all patients with GS, with cholecystitis being the commonest (61%). The GS prevalence by population group was significantly higher in the white population which was an independent risk factor [adjusted OR 2.44(1.86-3.20)]. Other independent risk factors for GS were female gender [adjusted OR 1.97(1.51-2.56)] and increasing age [adjusted OR 1.03(1.02-1.04)].

Conclusion. In this hospital based study, the prevalence of GS among adult patients was slightly higher than in other previous African studies. Independent risk factors for GS were increasing age, white race and female gender. Further community based surveys are necessary to determine the true prevalence of GS among adults in South Africa.

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GS	Gallstones
USS	Ultrasound Scan
BMI	Body Mass Index
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
USA	United States of America
UK	United Kingdom
SEC	Socio-economic Class
SD	Standard Deviation
HRT	Hormone Replacement Therapy
WHO	World Health Organisation
CI	Confidence Interval
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
HAART	Highly Active Antiretroviral Treatment
FPG	Fasting Plasma Glucose
BP	Blood Pressure
HDL	High Density Lipoprotein
OGTT	Oral Glucose Tolerance Test
ERCP	Endoscopic Retrograde Cholangiopancreatography
LFT	Liver Function Test
TPN	Total Parenteral Nutrition

MRCP	Magnetic resonance cholangiopancreatography
EUS	Endoscopic Ultrasound
CT	Computed Tomography
GP	General Practitioner
MICOL	Multicentrica Italiana COLelitiasi
HMG-Co A	3-hydroxyl-3-methyl-glutaryl co-enzyme A
UDCA	Ursodeoxycholic acid
ESWL	Extracorporeal Shock Wave Lithotripsy

Chapter 1: Introduction

1.1 Introduction

The chapter begins with a general overview of gallstones (GS). Details of the pathophysiology, risk factors and clinical presentation of GS are subsequently explored. The change in the risk factors for GS over time and the possible implications thereof on the prevalence of GS in South Africa are discussed. The published literature on various aspects of GS is reviewed and the chapter concludes with a description of the aims and objectives of the study.

Bile is an important physiological fluid of the human body that is synthesised by hepatocytes in the liver (1). It is stored in the gallbladder, an abdominal organ that lies beneath the liver. (See Figure 1.1)

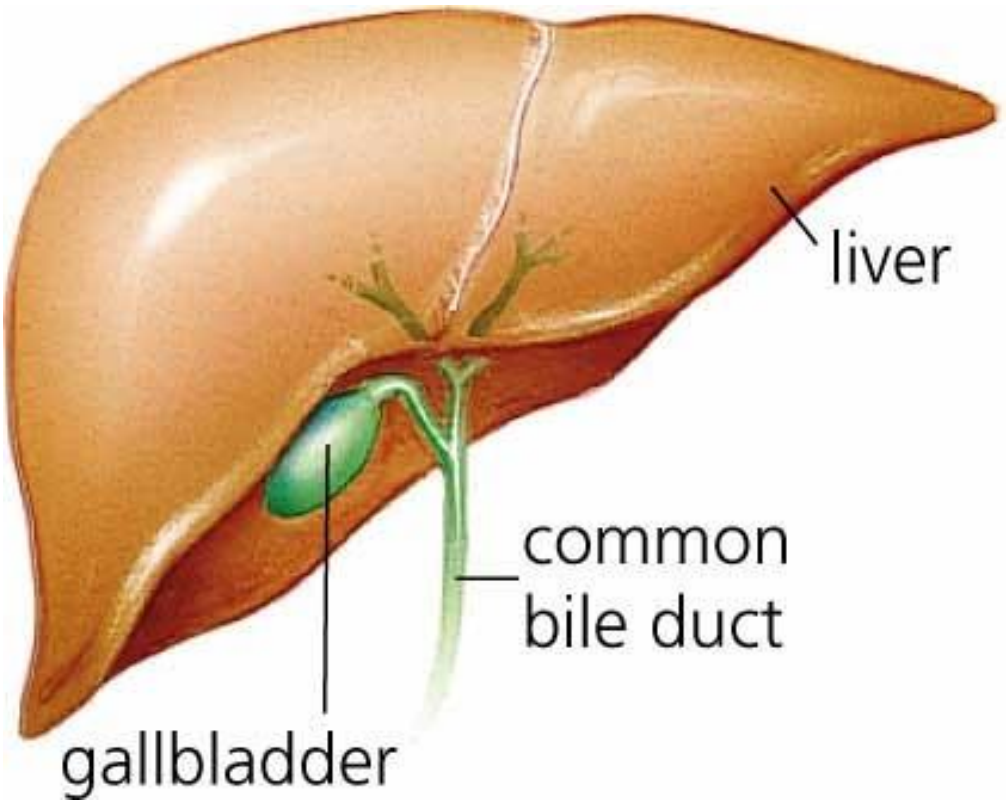

Figure 1:1 Anatomy of the liver and gallbladder.(Adapted from Seeds of life)(2)

Bile predominantly consists of 97% water. The other 3% is made up of bile salts, phospholipids, cholesterol and other constituents (1,3). (See Figure 1.2)

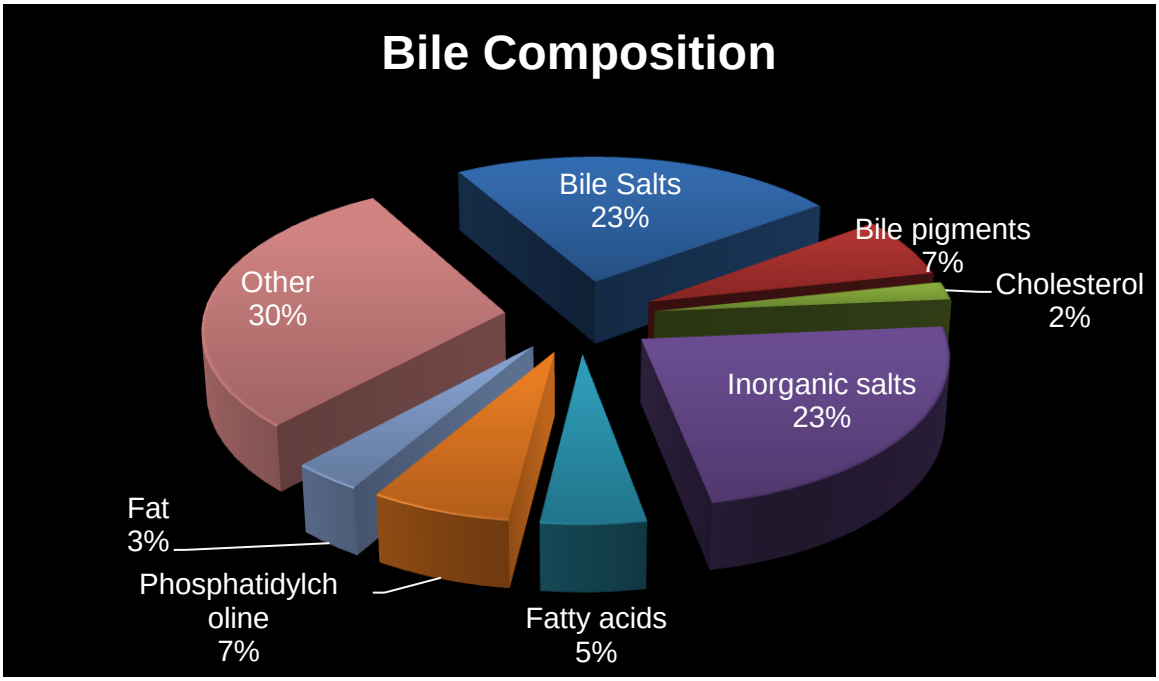

Figure 1.2: The composition of bile (excluding water)

Bile has several physiological functions in the body which include:

(i) Excretion of potentially harmful lipophilic substances such as exogenous drugs and environmental toxins as well as endogenous substances such as bilirubin and bile salts (4,5).

(ii) Digestion of fat through the emulsification of dietary lipids by bile salts which are contained in the bile, thus facilitating intestinal absorption of fat (3,4,6).

(iii) Cholesterol excretion. Bile salts are synthesized from cholesterol and bile is the major route by which the body excretes cholesterol (4,6).

(iv) The excretion of immunoglobulin A (IgA) and inflammatory cytokines. These once excreted in bile stimulate the innate immune system in the intestine which protects against enteric infections (4).

(v) Bile salt reabsorption in the distal small bowel. This is known as the entero-hepatic circulation and is the main route of absorption of fat dependent dietary micronutrients such as Vitamin A, D, E and K (3,4,6).

In the gall bladder, the bile salts and phospholipids form micelles around cholesterol molecules. This keeps cholesterol in a soluble state and maintains bile in liquid form (3). The equilibrium of bile constituents can be altered through various intrinsic and environmental factors (7). (See Figure 1.3) Disturbances in this balance results in the precipitation of one or more of the bile constituents leading to the formation of gallstones (GS) (8).

Gallstones have been part of human pathology since ancient times. Archaeological data documents GS in mummified bodies of ancient Egyptian and Japanese royalty from 1 400 BC (9,10). Today, GS are a common health disorder especially in western countries (11,12). They are the leading cause of in-hospital admissions amongst all digestive disorders in the United States of America (USA) (11,12). About US$6.5 billion is spent annually in the (USA), in direct hospital related costs as well as indirect costs such as employee absenteeism and poor quality of life for those affected (13).

Gallstones are classified into cholesterol, pigment and rare stones (3). This classification is based on the predominant chemical composition and gross appearance of the GS (3). Cholesterol rich stones are the commonest and constitute about 75% of all GS. (See Figure 1.4) They are predominantly made up of cholesterol crystals, with varying amounts of calcium bilirubinate, calcium carbonate and calcium phosphate. Pigment stones are made up of calcium bilirubinate. Pigment stones are further sub-classified into black and brown pigment stones. Black stones make up approximately 20% of all GS while brown stones account for just 4.5%. Rare stones are made up of calcium carbonate stones and fatty acid-calcium stones (3).

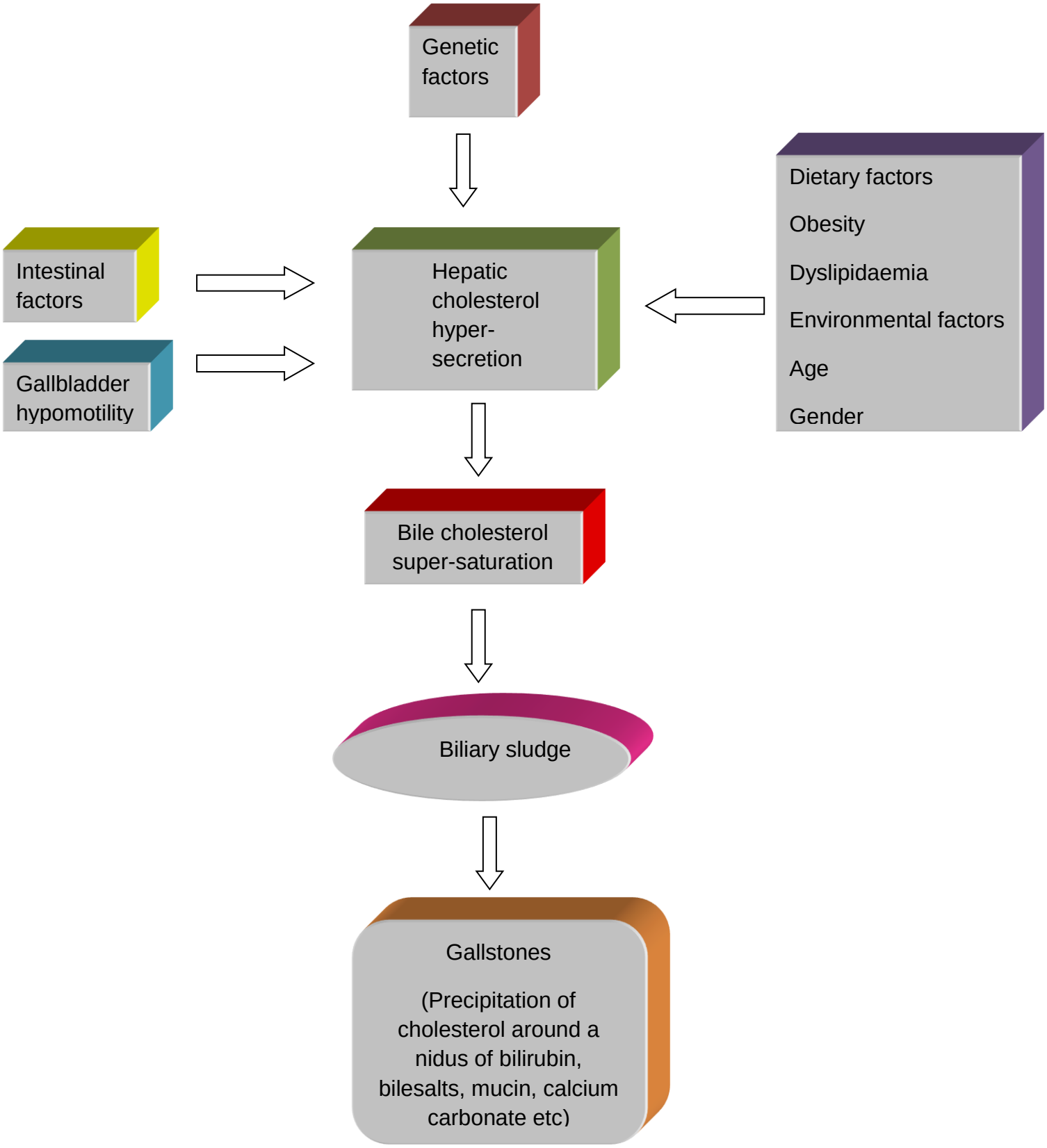

Figure 1.3: Pathogenesis of gallstones (Adapted from Premkumar *et al*) (7)

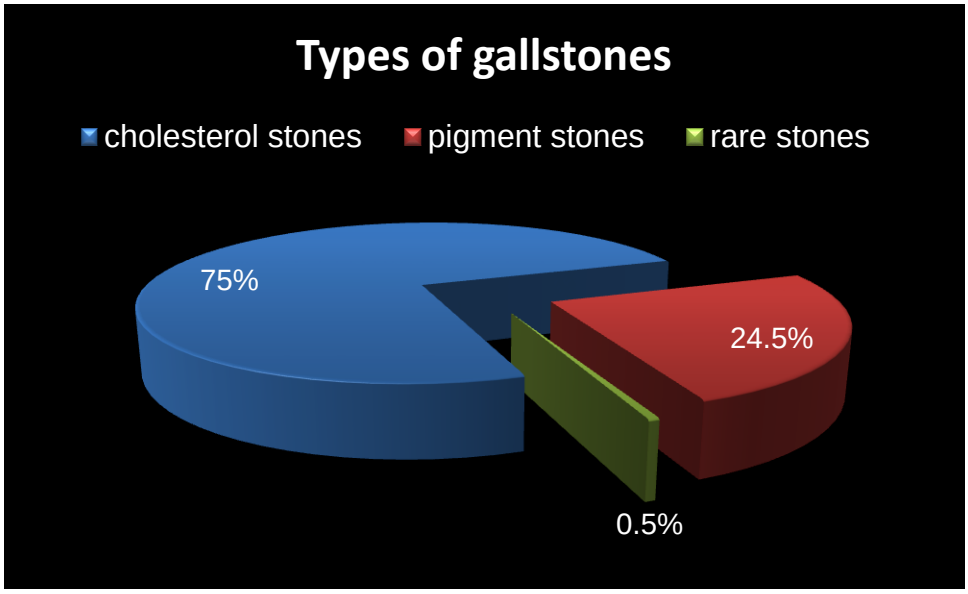

Figure 1.4: Types of gallstones.

1.2 The pathophysiology of GS

The pathophysiology of GS differs with each GS subtype. Black pigment stones typically form in the gallbladder. They are formed when bile becomes supersaturated with bilirubin monoconjugates. The monoconjugates then precipitate with calcium ions to form calcium rubinate (14–16).Black pigment GS are commonly associated with clinical scenarios in which hyperbilirubinaemia (the availability of large quantities bilirubin conjugates from haemolysis) is a predominant feature. These clinical conditions include sickle cell disease and ineffective erythropoiesis among others (11).

Brown pigment stones form in the bile ducts and are more common in Asia where they are associated with infection of the biliary system by bacteria or parasites. In the west they may occur in the presence of malignant biliary strictures or inflammatory strictures as a result of prior biliary system instrumentation e.g. cases of previous endoscopic retrograde pancreatography (ERCP) (11,15).

Cholesterol GS are formed when there is super-saturation of bile with cholesterol. This results in the formation of cholesterol micro-crystals in the gallbladder (3,8). These micro-crystals deposit around a nidus of bile pigment precipitants or mucus proteins forming gallstones that may enlarge over time (3,17).

1.3 Risk factors for developing gallstones

There are multiple established risk factors for developing GS which are shown in table 1.1.

Table 1.1: **Risk factors for developing gallstones** (Adapted from Stinton *et al*) (11)

Non modifiable risk factors	Modifiable risk factors
Family history	Metabolic syndrome(Obesity/dyslipidaemia/diabetes)
Genetic predisposition	Sedentary lifestyle
Female gender	Rapid weight loss
Ethnicity	Pregnancy
Increasing age	High fat diet
	Cirrhosis
	Crohn's disease

1.3.1 Non modifiable risk factors

1.3.1.1 Family history & genetic predisposition

While no distinct mendelian pattern of GS inheritance has been clearly shown, it is apparent that genetic susceptibility is an important determinant in gallstone disease (18).Studies have shown up to five times increased risk of developing GS in relatives of GS patients (19,20). A study on 43 141 pairs of twins in Sweden showed significantly higher GS in monozygotic versus dizygotic twins (concordance rate 12% versus 6%) (20,21).This could have resulted from shared environment being a possible mechanism. However this was eliminated by data from studies which showed that spouses of affected patients do not have any increased risk of GS (22).

Mutations in the multidrug resistant protein (MDR3/ABCB4) and cholesterol 7 a hydroxilase (CYP7A1) genes are associated with a specific type of cholesterol gallstone disease which is characterised by low phospholipid levels (23–26).The low phospholipid levels result in precipitation of cholesterol micro-crystals in bile (3). However, these genetic mutations are only responsible for a small proportion of cholesterol GS (23–26).

1.3.1.2 Female gender

Gallstones tend to be commoner in females than males (11).This has been attributed to the female hormones oestrogen and progesterone. Oestrogens stimulate hepatic lipoprotein receptors as well as the enzyme 3-hydroxyl-3-methyl-glutaryl co-enzyme A (HMG-Co A) reductase (27,28). This is the enzyme that catalyses the rate limiting step in cholesterol synthesis. These oestrogen induced changes result in increased synthesis of cholesterol by the liver (28). Progesterone causes impaired gallbladder emptying leading to stasis which promotes GS formation (3,27,28). Use of hormonal contraception and hormone replacement therapy (HRT) also increase the risk of gallstone formation (27).

1.3.1.3 Ethnicity

The prevalence of GS varies with ethnicity (11). Table 1.2 shows the difference in GS prevalence among various ethnic groups according to community based ultrasound studies. More importantly the table also shows the difference in GS prevalence among different ethnic groups from the same country i.e. USA. It is plausible that the general national GS prevalence of a particular country may not necessarily be an accurate reflection of GS prevalence among specific ethnic groups (population/racial groups) in that same country. There is a possibility that ethnicity may confer a yet unknown genetic risk.

Table 1.2: Gallstone prevalence according to ethnicity (Adapted from Shaffer E) (12)

Ethnic group	Female prevalence	Male prevalence
American Indians	64.1%	29.5%
White Americans (non Hispanic)	16.6%	8.6%
Black Americans	13.9%	5.3%
Mexican American	26.7%	8.9%
Hispanic American	19.1%	5.4%
Mapuche Indians(Chile)	49.4%	12.6%

1.3.1.4 Age

The risk of GS increases with increasing age becoming 4-10 times more likely in individuals over the age of 40 years (11). This could possibly be as a result of other GS risk factors that also increase with age such as the metabolic syndrome. Older age also means longer exposure to other risk factors e.g. sedentary life style. Gallstones being a chronic disorder are also likely to increase with older age (29–32). Symptoms and complications of GS also increase with age leading to more cholecystectomies (32).

1.3.2 Modifiable risk factors

1.3.2.1The Metabolic Syndrome

The metabolic syndrome is associated with increased risk of developing GS as well as that of developing GS complications (11,33). Some researchers have advocated that GS should be considered a part of the metabolic syndrome due to the very strong association (34,35).The metabolic syndrome consists of a constellation of clinical features. According to the International Diabetes Federation (IDF) definition, for a person to be defined as having the metabolic syndrome they must have:

- Central obesity defined by ethnic appropriate values for waist circumference* plus any two of the following four factors:

Raised triglycerides	**≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality**
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Raised blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose	(FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

*If BMI is >30kg/m², central obesity can be assumed and waist circumference does not need to be measured. **FPG**: fasting plasma glucose **BP**: blood pressure **HDL**: high density lipoprotein **BMI** body mass index **OGTT**: oral glucose tolerance test

Table 1.3: The IDF definition of the metabolic syndrome. (Adapted from the International Diabetes Federation) (36)

1.3.2.1.1 Obesity

Gallstones are common in morbidly obese individuals with at least a quarter of them harbouring GS (37). The greatest risk of GS in obese individuals has been noted in the late teenage years and lean body mass has been shown to protect against GS (38,39). There is also some evidence that BMI correlates with GS more in females than it does in males (40,41). Adult females with high BMI have a greater risk of developing GS compared to males of equal BMI (42).Researchers have proposed that this could result from males having a leaner body mass than would females for the same BMI (43–45).

Individuals with obesity have increased gallbladder volumes as well as increased HMG-Co A reductase activity.This results in increased liver synthesis of cholesterol and its subsequent secretion into bile thus encouraging GS formation (40,41,46–48).

1.3.2.1.2 Dyslipidemia

Low High Density Lipoprotein (HDL) cholesterol and elevated triglycerides are associated with increased risk of developing GS (44,49,50). However there is no definite association between hypercholesterolemia and GS (38,51). There is some evidence that the use of statins for treating dyslipidaemia reduces the risk of developing GS, though more work is needed to confirm this finding (52).

1.3.2.1.3 Diabetes

In insulin resistance as well as overt diabetes there are changes to gallbladder and bile physiology which increase the likelihood of developing GS. These include:

- easy cholesterol super-saturation of bile secondary to impaired bile salt synthesis
- enhanced cholesterol secretion
- reduced ejection fraction of the gallbladder secondary to gallbladder hypomotility
- Increased volume of the gallbladder in fasting phase (53–58).

1.3.2.1.4 Hypertension

There is evidence that hypertension is associated with GS (59,60). A study in China which consisted of 918 patients with GS and 6652 healthy controls showed that systolic blood pressure and diastolic blood pressure were significantly higher in patients with GS compared to the controls (61).The exact mechanism by which hypertension increases GS risk remains unclear (61).

1.3.2.2 Sedentary Lifestyle

A sedentary life style increases the risk of gallstone disease whereas increased physical activity decreases this risk (11). This effect is independent of the role of physical activity in weight loss (62,63). In a study of 25 639 volunteers aged 40-74 from England, increasing endurance exercise to 30 minutes, 5 times weekly was associated with a 70% decreased risk of symptomatic gallstones(64). The exercise induced reduction in symptomatic GS has been linked to lower rates of cholecystectomy amongst asymptomatic GS careers (62,65).

1.3.2.3 Rapid Weight Loss

Between 30% and 71% of individuals who undergo rapid weight loss due to calorie restriction or bariatric surgery develop GS(66–72).Rapid weight loss, especially that exceeding 1.5kg/week increases risk of GS through increasing cholesterol secretion by the liver, increasing mucin production by the gallbladder as well as reducing gallbladder motility (3,8).

1.3.2.4 Pregnancy and Parity

High oestrogen levels in pregnancy lead to increased cholesterol secretion and formation of supersaturated bile. Increased progesterone levels decrease gallbladder motility which results in increased gallbladder volume and bile stasis (28). All these changes promote GS formation. Increased parity probably increases risk of GS by repeatedly exposing a woman to the above mentioned changes (3,27,73).

1.3.2.5 Diet

Gallstone prevalence is higher is communities that have calorie dense diets that are rich in cholesterol and saturated fatty acids (3). The shift towards a more westernized diet among the Japanese was associated with a shift in the prevalent gallstones from pigment to cholesterol type (74).This phenomenon was also noted after World War II in Europe(38,75,76).Not all individuals develop cholesterol GS as

a result of these dietary changes and genetic variations in cholesterol metabolism may account for this(77,78).

1.3.2.6 Total Parenteral Nutrition (TPN)

Gallbladder emptying is stimulated by the presence of food in the duodenum(3). Parenteral nutrition involves the infusion of nutrients directly into the blood stream. This bypasses the intestines thereby removing enteric stimulation of the gallbladder. This ultimately results in gallbladder stasis and formation of GS (79).

1.3.2.7 Underlying Chronic Disease

1.3.2.7.1 Cirrhosis

Gallstones are about 25% more common in cirrhotic patients when compared to the normal population (80).In liver cirrhosis there is altered hepatic bilirubin secretion and reduced gallbladder motility which makes cirrhotic patients prone to GS. Pigment stones are the commonest type of GS that cirrhotic patients develop (3,80).

1.3.2.7.2 Chron's disease

Chron's disease is an idiopathic inflammatory bowel disorder. When it involves the terminal ileum, it causes a reduction in bile acid re-absorption. This results in reduced enterohepatic circulation of bile acids. There is an increased ratio of cholesterol to bile acid secretion by the liver resulting in cholesterol super-saturation of bile and the consequent formation of GS (8,81).

1.3.2.7.3 Other diseases

In cystic fibrosis, bile acid binds to undigested nutrients in the bowel. This reduces the enterohepatic circulation of bile acids and increases the risk of GS by 10%-30% in a mechanism akin to that observed in Crohn's disease (82). Chronic haemolysis such as that observed in sickle cell disease, leads to excessive bilirubin excretion with the formation of black pigment stones (11). The risk of developing GS in individuals with spinal cord injury is threefold that of the general population (83–85). This probably arises from gallbladder stasis and reduced bowel motilility which alters bile acid metabolism (11).

1.3.2.8. Drugs

Somatostatin analogues such as octreotite inhibit cholecystokinin release which causes gallbladder hypomotility and stasis of bile (86). Half of patients receiving

octreotide develop GS (87,88). Thiazide diuretics cause biliary cholesterol saturation thus increasing the risk of GS formation (89).

1.4 The Natural History of Gallstones

More than 80% of individuals with GS remain asymptomatic throughout their lifetime (90). A small percentage of up to 4% develop symptoms annually and up to 10% become symptomatic after 5 years of follow up (90–92). Major gallstone complications develop in only 1-2% per year (3,74,93).The longer the individual harbours GS the less likely they are to develop symptoms. However symptomatic GS in older individuals are more likely to complicate when compared to younger individuals (32,90).

1.4.1 Clinical Presentation of Gallstones

Gallstones can cause clinical symptoms through a myriad of ways. (See Figure1.5) Intermittent obstruction of the cystic duct may cause biliary pain which is the commonest manifesting symptom of GS (3). It typically is epigastric or right upper quadrant pain that may be associated with nausea or vomiting. This pain can last for a few hours but may persist for up to 24 hours (3,8).

Inflammation of the gallbladder as a result of infection arising from an obstructed cystic duct is known as acute cholecystitis. In these cases patients may have fever in addition to biliary pain (8). Cholecystitis is often preceded by one or more prior episodes of biliary pain which may be confirmed on history taking (3). Recurrence is common if cholecystitis resolves without surgical intervention (3,94).

Sometimes a stone impacts in the gallbladder neck or cystic duct and obstructs the common bile duct. This is termed the Mirizzi syndrome (8). Choledocholithiais and cholangitis are as a result of a stone in the bile duct causing bile stasis and bacterial super-infection (3).

A gallstone impacting at the level of the ampulla can cause backpressure on the pancreas. This then leads to the premature release of pancreatic enzymes resulting in pancreatitis (3).

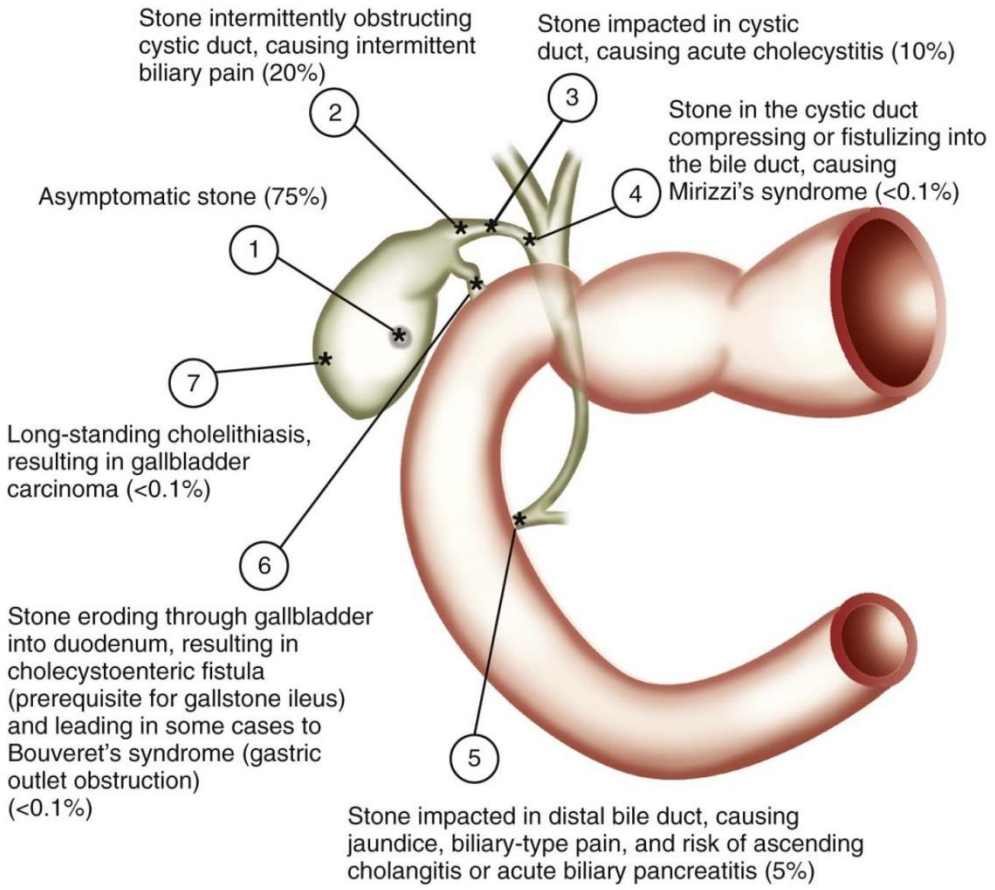

Figure 1.5: Clinical syndromes arising from gallstones (Adapted from Wang *et al*) (3)

Longstanding GS may result in gallbladder cancer in less than 0.3% of patients with GS

Other less common complications of GS include:

•Gallbladder mucocoele

•Gallbladder empyema

•Gangrenous gallbladder

•Biliary peritonitis

•Porcelain gallbladder

•Gallstone ileus (3,8,95)

1.4.2 Diagnosis of Gallstones

The principal diagnostic modality for diagnosing GS is abdominal ultrasound scan (USS). It is relatively cheap, easy to perform, accurate, readily available and does

not expose patients to radiation (3,96). It has a sensitivity of more than 95% for stones larger than 2mm and a specificity of more than 95% when stones produce acoustic shadows (97). Liver function tests (LFTs) together with abdominal USS are important initial tests and should be offered whenever there is clinical suspicion of GS disease e.g. where a patient presents with abdominal pain, jaundice or fever (98) However, LFTs are not reliable and may be normal in the presence of symptomatic disease (99).

Abdominal X-ray is of limited use in the diagnosis of GS. Only 50% of pigment stones and 20% of cholesterol stones are radio-opaque (3). With cholesterol stones being the commonest GS, use of X-ray in diagnosing GS would miss most of them (3). Computed Tomography (CT) scanning is suitable for investigating GS complications such as abscess, perforation or pancreatitis. It is less suitable for uncomplicated GS as it is expensive and exposes patients to radiation without adding more value than would be obtained though ultrasound imaging (3,8).

Magnetic Resonance Cholangio-pancreatography (MCRP) is rapid and non invasive and shows immense biliary tract anatomical detail (3). It is therefore useful where choledocholithiasis is suspected. It is also recommended where ultrasound is suboptimum as a result of overlying bowel gas, large body habitus or other operational technical challenges (3,8,100).

Endoscopic retrograde cholangio-pancreatography (ERCP) involves instrumentation of the biliary tract system. It is used more for treating confirmed choledocholithiasis than for initial GS investigation (98). Its major drawback is the development of complications such as pancreatitits which can be fatal (3). Prudent selection of patients for ERCP is therefore vital.

Endoscopic ultrasound (EUS) is a non-invasive test that is highly accurate in detecting bile duct stones (3). It has limited availability in most non referral centres as its high sensitivity for detecting gallstones depends on highly experienced operators who may not be readily available (3,8).

1.4.3 Management of Gallstones

Asymptomatic GS do not need any intervention except in some unique patient groups at risk of complications or malignancy such as those with porcelain gallbladder, immunosupressed patients (e.g. after transplantation) and elderly diabetics (101).

The definitive management for symptomatic GS is a laparascopic cholecystectomy (3). It can be performed either at the time of presentation or after the acute presenting clinical episode has resolved (3,8). Where patients are unfit for surgery or are unwilling to undergo surgery, medical therapy such as extracorporeal shock wave lithotripsy (ESWL) or bile acid dissolution therapy with ursodeoxycholic acid (UCDA) may be used. Ursodeoxycholic acid reduces biliary cholesterol secretion, increases biliary bile acid concentrations, and consequently reduces the cholesterol saturation index. It also inhibits biliary secretion of cholesterol, reduces intestinal absorption of cholesterol, increases hepatic bile secretion, and improves gallbladder emptying(15).

Extracorporeal shock wave lithotripsy utilises high energy shock waves generated by an electrical discharge to fragment GS (102). Both UDCA and ESWL are however less successful when compared to cholecystectomy. Therapy with UDCA and ESWL is only successful in 27% and 50% of patients respectively (15). Approximately 40% of patients will have recurrence of GS when treated with these non surgical interventions (103,104). Where patients present with choledocholithiasis, ERCP prior to cholecystectomy is recommended to clear the bile duct of stones (8).

Although sustained weight loss and increased physical activity can help in preventing the development of gallstones they are of little benefit in those with symptomatic GS (62).

1.5 South African Background

South Africa has a population of 51.8 million people. Females make up just over half of this population at 51.3% and males constitute the remaining 48.7%. The population is generally young with a median age of 25 years. The racial distribution amongst the general population of South Africa is Blacks 79.2%, Whites 8.9%, Coloureds 8.9% and Indian/Asian 2.5% (105). Urbanisation in South Africa has

increased. This is evidenced by an increase in the proportion South Africans living in urban areas from 56.3% in 2001 to 64% in 2014 (106,107).

Obesity is highly prevalent in South Africa. About 70% of South African women above the age of 37 years are overweight or obese (108). A Lancet survey published in 2013 also showed that 69.3% of South African women above the age of 20 years are either overweight or obese and 42% of them are obese (109). Diabetes and dyslipidaemia have also been increasing among studied urban South African populations (110–112). In a study by Levitt *et al* the proportion of life spent in an urban area was an independent risk factor for developing diabetes among South Africans living in urban areas. (110)

South Africa also has one of the highest HIV/AIDS burdens in the world. There are about 7 million South Africans living with HIV/AIDS (113). About one fifth of South African women in their reproductive age are HIV positive (114). The use of highly active antiretroviral treatment (HAART) especially the protease inhibitors is associated with the development of lipodystrophy, dyslipidaemia and truncal obesity with insulin resistance which may progress to overt diabetes (111,115). Dyslipidaemia, obesity and the metabolic syndrome will likely increase over time as more South Africans access HAART.

Physical inactivity is common among South African adults, with 48% of men and 63% of women being classified as inactive in a Department of Health survey (116). Over time the South African diet has changed towards a more westernized calorie dense diet with a high fat content (116,117). All these factors interplay in increasing the risk of developing GS in the South African population.

1.6 Literature Review

1.6.1 Prevalence of Gallstones

Ultrasound based surveys have shown varying gallstone prevalence across the world .Gallstones tend to be commoner in the western world and less common in Asian and African countries. (See Fig 1.6)

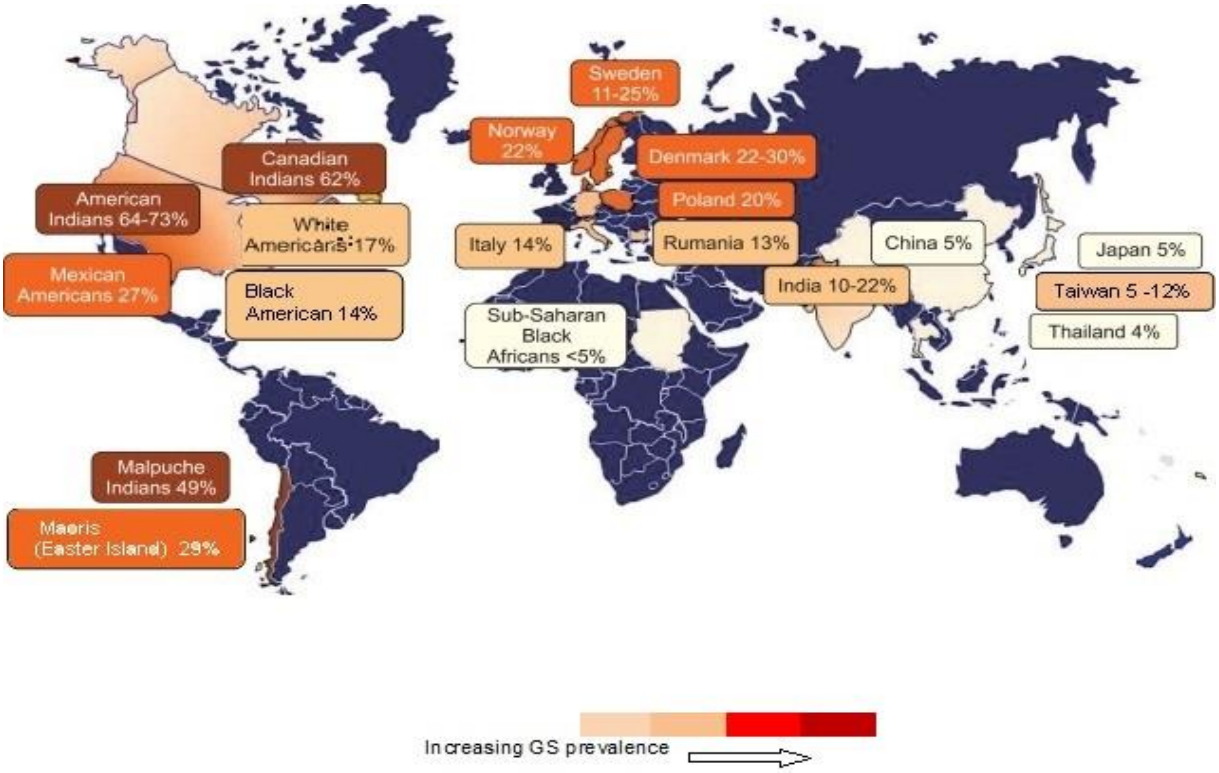

Figure 1.6: Female worldwide gallstone prevalence based on ultrasound surveys (Adapted from Stinton L) (11)

A population based ultrasound survey of gallstones was carried out in the USA as part of the third National Health and Nutrition Examination Survey (NHANES III). Over 14 000 participants made up the representative sample that was examined. The overall GS prevalence was 7.9% for men and 16.6% among women. The study sample was diverse and is one of the few studies that explore GS prevalence among different ethnic groups in the world. The highest GS prevalence of 26.7% was seen among Mexican American women and the lowest of 5.3% was noted among Black American males. Prevalence was as high as 76.1% in American Indian women over the age of 65 from Arizona. In this study GS prevalence was higher with full- Indian heritage than in those with mixed heritage (118).

Gallstone prevalence in Europe is comparable to that in the USA with the mean European prevalence at 18.5% (99). The lowest prevalence of 5.9% was reported in Italy while the highest of 21.9% was recorded in a Norwegian study that looked at 2 464 individuals between the ages of 20 and 70 years (119,120).

In South America a study in Peru showed an overall prevalence of 14.3% while two Argentine studies found prevalence of 20.5% and 21.9%. Amerindian genetic admixture may be responsible for this high GS prevalence. Data from Chile documents GS prevalence of 67% and 45% among Mapuche Indian females and males respectively (121–124).

Data from Asian studies conducted in Japan, Taiwan, China, Bangladesh and India showed GS prevalence ranging from 3.2% to 22.87% (42,125–131). Prevalence was generally low in these studies with the highest prevalence of 22.87% being observed in a selected sub-population that had multiple modifiable risk factors for GS (127). In the Middle East, data from two Iranian studies showed prevalence of 0.8% and 4.7% (132,133).

Earlier post mortem based studies in Africa failed to show any GS (134). This literature was based on the Masaai tribe of northern Kenya and southern Tanzania. The Masaai are a unique group of people who are nomads and are not exposed to most GS risk factors (11). Therefore this study result cannot be generalised to all African populations. Since the study was post-mortem based, GS prevalence among the living was not explored.

There are few community based ultrasound surveys in Africa probably as a result of the lack of funding and unavailability of multidisciplinary personnel required to conduct such studies. One such study conducted in Sudan showed a GS prevalence of 5.2% (135).The study however had a small sample size of 242. In Tunisia, a study of 1 123 adults from a small town in central Tunisia showed GS prevalence of 4% which is lower than western based studies (11,136). Data from hospital based ultrasound studies in Africa shows prevalence of 2.9%, 5.9% and 5.2% for Nigeria, Ghana and Ethiopia respectively (137–139). In South Africa a survey of 100 black elderly women from Soweto showed a GS prevalence of 10% (140).

1.6.2 Risk Factors for Gallstones

1.6.2.1 Gender

Data from multiple studies shows that GS are more common in females than they are in males (118,122–124,131). However two studies from Taiwan showed a different result with no significant difference in GS prevalence between males and

females (42,126). A large study in China of over a million adults who were mostly urban government and local company employees, showed an overall GS prevalence of 4.6%, with males having a statistically significant higher prevalence than females. (141). Males also had more GS than females in a study by Nomura *et al* in Japan (125).These findings are different from western studies where the predominant type of GS are cholesterol stones(3). Asian studies have shown that pigment stones are commoner than cholesterol stones in this part of the world (11,127).Since pigment stones are associated with biliary tract bacterial and parasitic infections there is unlikely to be a gender difference in the prevalence.

1.6.2.2. Family History

An Italian study found a significantly higher prevalence of GS in 202 first degree relatives of GS patients compared to controls (19). This is in keeping with other studies done in Argentina, India and Taiwan (42,123,130). The study in Peru found that there was a higher likelihood of GS if there was another person from the same household who also had GS (122). This could have resulted from possible genetic risk or shared environmental risk factors. A French study of 1 322 subjects did not find an association between family history and GS (142). This suggests that there are more complex factors involved in gallstone formation other than a positive family history alone.

1.6.2.3 Pregnancy and parity

Data from western countries shows that 12% of pregnant women develop GS and 1-3% of these women develop complications that require surgery (28). A study conducted in Nigeria showed different results with only 2.9% of women attending an antenatal clinic having GS on ultrasound and just 0.2% of them developing complications (137). This low prevalence could have resulted from the study being carried out in a setting of a low general GS prevalence compared with western based studies (11,12).

Walker *et al* described a higher prevalence among Sowetan women compared to that described for Nigerian women by Ibitoye *et al*. (137,140). This difference may be explained by the fact that women attending the antenatal clinic were younger, premenopausal women (age range 14 - 43 years) and may have had lower parity unlike the population studied in Soweto who were older (age range 55 - 85 years)

and possibly had higher parity. Increasing age and parity are risk factors for developing GS (11). Parity was shown to be a risk factor for GS in studies conducted in Peru, North India and Sweden (122,130,143). However a French study showed that parity was not a risk factor for GS (142). The definition of parity used in the French study was 'one or more pregnancies' as opposed to other studies that differentiated degree of parity such as the Peruvian study which showed that parity of greater than 4 significantly increased GS risk (122). A higher parity probably increases a woman's duration of exposure to the lithogenic hormonal changes associated pregnancy.

1.6.2.4 Oral Contraceptive Pill (OCP)

Use of the OCP was reported as a risk factor for GS in studies conducted in Sweden, Peru and Taiwan however literature from France does not support this finding (42,122,142,143). The French study excluded women who were under 30 years old and as such excluded a significant proportion of women using OCP and this may have impacted their results (142).

1.6.2.5 Diabetes

A number of studies have shown an association between diabetes and GS (42,130,133). A study of 889 diabetic patients in Italy showed an overall GS prevalence of 30.4% (15.5% for males and 38.6% for females) (144). This as expected was much higher than that of the general Italian population shown in the Multicentrica Italiana COLelitiasi (MICOL) study which showed a prevalence of 6.5% males and 10.5% for females respectively. Agunloye *et al* found a GS prevalence of 17.5% among Nigerian diabetic patients (145). This is much lower than that seen in the Italian diabetic patients perhaps because the background GS prevalence of African countries is generally lower than that of western countries (11,12).

There are some studies that have shown no association between diabetes and GS. These include a study of 1 322 individuals from Southeast France and another one of 1 721 vegetarian volunteers of the Buddhist Tzu Chi Foundation in Taiwan (126,142).

1.6.2.6 Obesity

The study in Tunisia concluded that there was no association between BMI and GS (136). This is unlike the conclusions drawn from multiple studies from the UK,

France, Argentina and Nigeria (64,124,136,142,145).The definition of obesity used in the Tunisian study was: BMI > 27kg/m^2 in males and BMI > 25kg/m^2 in females (136). However, obesity is defined by the World Health Organisation (W.H.O.) as a BMI > 30kg/m^2 (146). There were very few participants in the study who met this widely accepted definition of obesity. This could explain the different findings in this study regarding the relationship between BMI and GS when comparing with other studies. The French study also did not find an association between obesity and GS which again contradicts most literature (142).

1.6.2.7 Dyslipidaemia

Studies show conflicting data on the relationship between dyslipidaemia and GS. A Swedish study by Halldestam *et al* and a Chinese survey of the Uinghur ethnic group showed a strong relationship between hypercholestrolaemia and GS(127,147). This finding is opposed to data from a Swedish study by Borch *et al* as well as data from Argentina (124,143). In their study from Norfolk, Banim *et al* described high HDL cholesterol levels as protective against GS and that hypertriglyceridaemia was associated with GS, a finding that was also documented by Alfredo (64,124).The use of lipid lowering statins to treat dyslipidaemia have been associated with a reduced risk of developing GS (52).

1.6.2.8 Diet

A Chinese study compared GS prevalence between two ethnic groups. Their results showed that the Uinghur Chinese had a GS prevalence of 22.87% while that of the Han Chinese was 11.64%(127).The differences between the two ethnic groups were probably due to environmental factors such as diet. The Uighur Chinese diet is more westernized with a higher fat and low fibre content which is known to promote GS formation (11). This was further supported by the finding that the Uighur Chinese developed more of cholesterol stones which were more frequently located in the GB. While the Han group mostly developed pigment stones in the intrahepatic ducts (127). Cholesterol GS have been linked to westernised diets (38,75,76).

In a study among urban based Taiwanese vegetarians, the GS prevalence was 8.2% which was higher than that of 5.0% found in a study that included non vegetarians from a Taiwanese village (42,126). The Taiwanese studies do not agree with literature that suggests that the high fibre content in vegetarian diets may protect

against GS formation (11,131).The increase in fried foods among urbanised Taiwanese vegetarians could account for the higher than expected GS prevalence among urban dwelling vegetarians (126).

1.6.2.9 Socioeconomic Classification (SEC)

There is conflicting data in literature regarding the relationship between SEC and GS. This likely stems from a lack of uniformity in the SEC determination methods used in the various studies. A study conducted in the USA among populations of differing SEC found an inverse relationship between GS and SEC (148). In a Bangladeshi study of 1 019 adults, GS were more common among those of middle to low SEC (128). This observation was also noticed in a British study by Murray et al (149).

The Chinese study carried out in Xinjiang, a predominantly low SEC region, yielded a higher GS prevalence compared to studies carried out in more affluent areas of China (127). Pigment stones which are more common in Asian countries are associated with biliary parasitic infections and are therefore likely to be more common in lower SEC regions where sanitation is likely to be poorer than in affluent regions.

However a study in the rural Gangetic basin of northern India showed that higher SEC was a risk factor for GS (130).A study conducted in rural Bangladeshi by Dhar et al also showed a similar result (129).It is possible that in these two studies a higher SEC may have been an indirect marker of a westernised lifestyle in a rural setting, which is associated with an increased the risk of developing cholesterol GS. Gallstone sub-typing was however not explored in these studies.

1.6.2.10 Drugs

There is some evidence that suggests that use of thiazide diuretics modestly increases the risk of GS formation. Leitzmann *et al* conducted a prospective study of 81 351 US women aged between 30 and 55 years who were using thiazide diuretics. Their results showed that the relative risk of cholecystectomy rose 36% and 57% for past and current thiazides users respectively (150).

1.6.3 Symptoms of Gallstones

The prevalence of symptomatic GS in population based studies was 6.3% and 9.21% in Britain and France respectively (142,151). In rural Bangladesh, 71.9% of

the study subjects were asymptomatic (129). These studies are in keeping with the natural history of GS (11). In hospital based studies such as Ethiopia the ratio of symptomatic to asymptomatic GS was 1:1(139).The high proportion of symptomatic GS in this study is probably as a result of a hospital based study having a higher likelihood of including more symptomatic patients than would a community based study.

In Chandigarh, India 64.9% of individuals with clinical symptoms suggestive of GS had GS confirmed on USS while in northern India only 7,12% of symptomatic individuals had confirmed GS (130,131). The difference in prevalence among symptomatic patients in these studies may arise from the different subjective terms used to describe symptoms in the studies.

In the Peruvian study abdominal pain, was an unreliable indicator of symptomatic gallstones. Symptoms were almost equally prevalent in subjects with GS and those without GS at 13.2% and 15.4% respectively (122). Symptoms ascribed to GS such as right upper quadrant pain are not unique to GS alone and may arise from pathology in other abdominal organs such as the liver.

There is a gap in knowledge regarding GS prevalence in Africa and more so in South Africa. The increase in GS risk factors such as obesity, sedentary lifestyle and dietary westernization among South Africans raises concern as to whether the traditional view of GS being rare among Africans is still accurate (11).

1.7 Study Objectives

1.7.1 Aim of Study

The aim of this study is to describe the demographic, clinical and sonographic features of GS occurring in adult patients undergoing abdominal ultrasonography in the radiology department at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

1.7.2 Specific Objectives

The specific objectives of the study are:

i. To describe the patient characteristics of adults undergoing abdominal USS at CMJAH

ii. To determine the prevalence of GS in adult patients undergoing abdominal ultrasonography at CMJAH.
iii. To compare the characteristics of patients who have GS with those without GS on abdominal USS
iv. To investigate risk factors associated with GS
v. To calculate the ratio of symptomatic GS to asymptomatic GS among those diagnosed with GS.
vi. To explore the reliability of clinical symptoms in correctly identifying patients with symptomatic gallstones
vii. To determine the prevalence of complications among those with GS.

1.8 Hypotheses

i. The prevalence of GS in South Africa is higher than previously reported.
ii. Given that GS prevalence was lowest among Black Americans we expect a low GS prevalence amongst Black South Africans compared to other population groups in South Africa (12).

Chapter 2: Materials and Methods

Introduction

The study design, site, population and methodology are described in this chapter. The methods used for the selection of study participants are explained. The definitions of study variables are given. The measures taken to ensure quality data are also described. The chapter ends with a review of the data processing methods and ethical considerations.

2.1 Study Design

This study was a retrospective cross sectional analysis of the USS reports of all patients who underwent abdominal USS between January 1st 2009 and December 31st 2009.

2.2 Study Site

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is a quaternary academic institution for the University of the Witwatersrand Faculty of Health Sciences located in central Johannesburg. The institution has 1088 beds and serves as a referral centre for patients across the province of Gauteng as well as other neighbouring provinces of South Africa. It is estimated to have 4 000 professional and supporting staff offering a wide range of specialized services to inpatients and out patients (152).

2.3 Study Population

The radiology department at CMJAH performs an excess of 10 000 various ultrasound studies each year, a significant proportion of these being abdominal USS. This provided a large sample size which increased the power of our study. This study was the first hospital based study designed to investigate the prevalence of GS among patients presenting for abdominal USS at a quaternary health care institution in South Africa.

2.4 Study Sample

2.4.1 Sample Size Calculation

The sample size was calculated using the *sampsi* command in the STATA version 13 (STATA Corporation, College Station, TX) software package. A minimum sample size of 292 reviewed ultrasound reports was estimated to have 90% power to detect

a difference in prevalence of at least 5% using a one-sample comparison to a hypothesized value (p=0.052), with a 0.05 two-sided significance level (See appendix 1). The Ethiopian study with a prevalence of 5.2% was used in calculating the sample size as it is similar to the intended study (139). We however reviewed all abdominal USS reports done in the study period to allow for more precise estimates.

2.4.2 Inclusion Criteria

All adult patients (≥ 18 years at time of imaging) undergoing an abdominal USS at CMJAH department of radiology between January 1st 2009 and December 31st 2009 were included in the study.

2.4.3 Exclusion Criteria

i. Subsequent USS reports in a patient who had had more than one investigation were excluded.

2.5 Data Management

2.5.1 Data sources

To get an USS at CMJAH, the requesting physician manually completes an USS request form. (See Appendix 2) On this form the requesting physician documents the patient demographic details and the radiological investigation being requested. The completed form is then submitted to the radiology department where the patient's details are electronically captured into the medicom system to generate a unique X-ray number that is used to systematically file patient duplicate USS reports in the radiology department.

Medicom is an electronic record keeping system used by the Gauteng department of health at CMJAH. Demographic data including self reported race and SEC are captured when a patient is first seen at the hospital. This system generates unique hospital and X-ray numbers for each patient. The patient information can be retrieved from medicom by searching with the patients name and surname, hospital number or the X-ray number.

Once the USS is conducted the sonographer manually writes down the sonographic findings onto the USS request form. The original copy of this form is sent with the patient back to the requesting doctor and a hard copy of the same form is stored in the radiology department archives filing room. These archived reports were accessed and patient demographic details, the indication for the USS (based on the

patient clinical details supplied by the USS requesting physician) as well as the sonographic findings were extracted. The USS reports in most instances did not document the patient race, SEC and in some cases patient age. In these instances the patient name, hospital number or X-ray number was used to access the medicom electronic database to complete the missing information.

The medicom system uses the CMJAH classification and tariffs categories of 2006 for SEC stratification of patients which are based on personal or family income and assets. These categories classify patients into H0 (formally unemployed pensioners who do not pay any hospital fee), H1 (low SEC - annual income of less than R36 000), H2 (middle SEC -annual income of R36 000-R72 000), H3 (high SEC - annual income of R72 000 or more), emergency patients (life threatening emergency medical conditions and do not pay any hospital fees), medical aid patients and private ward patient (See Appendix 3).

2.5.2 Study Variables

Data was collected using a structured data collection sheet which is attached. (See Appendix 4) The following variables were collected and coded:

- Age was defined as the age in years of the patient at the time of undergoing USS. This was calculated from the date of birth and date of USS. In the absence of data that recommended categorisation of age, this variable was not stratified but rather collected as a continuous variable.
- Sex was defined as sex of the patient which was either male or female.
- Race was defined as the self identified race which the patient identified themselves as when demographic data was captured on the medicom system on the patient's initial visit to the hospital. Race in the medicom system is categorised as either White, Black, Asian or Coloured
- Ward was classified as either inpatients for patients being imaged from the hospital wards or casualty and outpatients for patients being imaged from the out patients department or other referring health care centres.
- Socio-economic class (SEC) was defined as per the CMJAH classification and tariff categories of 2006. (See Appendix 3)

- Date of imaging was the date the USS was done.
- Indication for sonar was considered related to GS if the requesting physician documented epigastric or right upper quadrant pain (with or without jaundice), a positive Murphy's sign, or if the requesting physician suspected GS. (See Appendix 4) An indication related to GS in a patient who subsequently had GS on that particular USS was interpreted as symptomatic GS. A patient who had GS on USS but whose indication did not meet the criteria considered for symptomatic GS above was classified as having asymptomatic GS. As over 60 different categories of USS indications were collected, they were grouped along similar clinical features and reduced to 14 groups to allow for data analysis. Indications that specifically pointed to GS and other biliary system pathology were grouped under biliary pathology.
- Gallstones were considered present if the sonographer documented with certainty the visualisation of GS on sonar. Where the sonographer was not certain or doubted whether GS were present or not, this was interpreted as absent GS.
- The site of GS was defined as the site of the visualised GS documented by the sonographer.
- Complications of GS were defined as documented sonographic evidence of known GS complications in a patient with sonograhic evidence of GS. They could either be cholecystitis, choledocholithiasis, cholangitis, pancreatitis or other complications which were further specified.

2.5.3 Data Quality Control

Data for the study was collected by the researcher who is a specialist physician and gastroenterologist. The researcher was assisted by the medical officers and interns who were attached to the gastroenterology unit. This was to allow correct interpretation of medical terms especially when capturing the indication for USS and when reading the ultrasound findings.

Missing data from the USS reports were completed by using the medicom system. This was necessary as all the USS reports did not document patient race and in cases where patient demographic data was manually entered by the requesting

physician there would be some missing data and this was commonly seen with SEC and date of birth. In patients who had multiple USS done, only data from the initial USS was captured. Where any handwritten patient data was conflicting, the medicom electronic system was considered the most accurate. Duplicates were identified and removed where appropriate.

2.5.4 Data Processing Methods and Analysis

Data was collected and coded using a Microsoft Office Excel 2007 spreadsheet. Categorical variables were described using frequencies. Normally distributed continuous variables were described using means and standard deviations and non-normally distributed continuous variables were described using medians and inter-quartile ranges. The overall prevalence of GS, the prevalence of asymptomatic, symptomatic and complicated GS were calculated using percentages. Exact binomial 95% confidence intervals (CI) were estimated for the overall GS prevalence.

Pearson chi squared test of proportions was used to compare characteristics of patients with GS and those without GS. The two sample T test was used to compare mean age of those with GS and those without. Using STATA version 13 (STATA Corporation, College Station, TX), unadjusted (univariate) and adjusted (multivariate) logistic regression models were fitted to explore risk factors for GS using the following factors: gender, race, age, SEC and type of ward. Results where appropriate will be reported as means +/- standard deviation.

2.6 Ethical Considerations

To protect the identities of participants, unique patient identifiers were used to replace patient names and hospital numbers. A separate sheet with patient identifying numbers corresponding to patient names was kept in an encrypted password protected file in the gastroenterology department. Patient names, hospital numbers and dates of birth were maintained after collecting data from the USS reports to allow completion of data by searching the medicom system. This was necessary to improve accuracy e.g. in situations where patients had similar names or missing hospital numbers etc. Patients with similar names were differentiated using hospital numbers and date of birth. These patient identifiers were however

removed from the data once data collection and cleaning was complete. The data was then analysed without any patient identifiers.

Data were stored in the student's personal laptop which has password restricted access. The information obtained from this study will be used to improve care at CMJAH and at other health care facilities in the country. Ethical approval was sought and was granted by the University of Witwatersrand Human Research Ethics Committee (medical). The ethics clearance certificate M140230 approved 25th May 2014 is attached. (See Appendix 5) Permission to carry out the study was sought and granted by the hospital authorities. Letter of approval is attached (See Appendix 6).

The study had originally been designed to include all USS reports done over a two year period however expert statisticians recommended that the study had reviewed an adequate number of USS over one year. This advice was based on the calculated minimum sample size of 292. (See Appendix 1) The relevant documents regarding this change of the study period to one year are attached. (See Appendix 7 and 8)

Chapter 3: Results

Introduction

In this chapter, the results of the study are presented with the aim of fulfilling the objectives of the study. This chapter initially describes the overall characteristics of the study sample before showing the prevalence rate of GS among the different study population categories. The prevalence of GS complications as well as a description of the type of complications found in the study is reported. The chapter concludes with a description of the patient characteristics that are associated with GS.

3.1 Study Sample Description

The overall description of the patients who were included in the study is shown in Table 3.1. A total of 3 494 USS reports were analysed and included in the study. Forty-four percent (1 524) were male and 1 965 (56.2%) were female and gender was unknown in 5 patients (0.1%). Most of the patients were Black 2 514 (72%) and race was unknown in 29 (0.8%) patients. The mean age was 47 +/- 17.5 years. Half of the patients 1 748 (50%) were in a low socio-economic class (H1).Nearly two thirds of patients (63.2%) were inpatients and the rest were outpatients. Indications for ultrasound imaging varied with the commonest being malignancy related pathology 571(16.3%). Only 4.4% of patients were scanned for specific biliary pathology. In 73 (2.1%) of the cases the indication for the ultrasound scan was unknown.

3.2 The Prevalence of Gallstones

The overall prevalence of GS was 8.1% (95% CI 7.2 - 9.1). (See Table 3.2) The prevalence of GS among females was significantly higher at 10.2% compared to the males at 5.5% with a male: female ratio of 1:2. Gallstone prevalence was significantly lowest in Black patients who had a prevalence of 6.1% compared to White, Asian and Coloured patients who had prevalence of 13.7%, 11.9%, 12.5% respectively. The mean age of patients with GS was a decade older at 56.4 +/- 17.5 years compared to those who did not have GS. Regarding socioeconomic classification, GS prevalence was highest among pensioners (H0)

Table 3.1 : Overall Patient Characteristics (N=3 494)

Characteristics	(n) (%)
Gender	
Male	1 524(43.62)
Female	1 965(56.24)
Unknown	5(0.14)
Race	
Black	2 514(71.95)
White	703(20.12)
Asian	160(4.58)
Coloured	88(2.52)
Unknown	29(0.83)
Age (years)	
Mean (SD)	46.95(17.46)
Socioeconomic class(SEC)	
H0(pensioners)	529(15.14)
H1(low SEC)	1 748(50.03)
H2(Medium SEC)	622(17.80)
H3(High SEC)	5(0.14)
Medical aid patients	441(12.62)
Emergency patients	36(1.03)
Private ward (Folateng)	111(3.18)
Unknown	2(0.06)
Ward	
Inpatients	2 208(63.19)
Outpatients	1 286(36.81)
Indication for ultrasound scan	
Malignancy work up	571(16.34)
Trauma & Post surgical complications	507(14.51)
Nephro-urogenital	477(13.65)
Liver pathology	424(12.14)
Abdominal pain/discomfort/tenderness	338(9.67)
Tuberculosis	249(7.13)
Gynaecological	203(5.81)
Sepsis/Ascites	186(5.32)
Biliary pathology	153(4.38)
Other	149(4.26)
Abdominalmass/distension/swelling/hernia	126(3.61)
Unknown	73(2.09)
Pancreatic pathology	20(0.57)
Splenic pathology	18(0.52)

Table 3.2: Patient Characteristics by gallstone status (N=3 494)

Characteristics	No Gallstones n (%)	Gallstones n (%)	p value for Pearson x^2 test
Gender			
Male	1 441(94.55)	83 (5.45)	< 0.001
Female	1 765(89.82)	200 (10.18)	
Race			
Black	2 361(93.91)	153(6.09)	<0.001
White	607(86.34)	96 (13.66)	
Asian	141(88.13)	19(11.88)	
Coloured	77(87.50)	11(12.50)	
Age Mean (Standard deviation)	46.12 (17.22)	56.39 (17.45)	<0.001*
Socioeconomic class(SEC)			
H0& Emergency patients	498 (88.14)	67 (11.86)	<0.001
H1(low SEC)	1 640(93.82)	108 (6.18)	
H2(Medium SEC)	581 (93.41)	41(6.59)	
H3 & Private ward	102(87.93)	14(12.07)	
Medical aid patients	387 (87.76)	54 (12.24)	
Ward			
Inpatients	2 048(92.75)	160 (7.25)	0.012
Outpatients	1 162(90.36)	124 (9.64)	
Indication for ultrasound scan			
Nephro-urogenital	435 (91.19)	42 (8.81)	<0.001
Gynaecological	193 (95.07)	10(4.93)	
Abdominal mass/distension/swelling/hernia	113 (89.68)	13 (10.32)	
Abdominal pain/discomfort/tenderness	295 (87.28)	43 (12.72)	
Trauma & Post surgical complications	504 (99.41)	3 (0.59)	
Sepsis/Ascites	179 (96.24)	7 (3.36)	
Liver pathology	385 (90.80)	39 (9.20)	
Pancreatic pathology	17 (85.00)	3 (15.00)	
Biliary pathology	112 (73.20)	41 (26.80)	
Malignancy workup	516 (90.37)	55 (9.63)	
Splenic pathology	17 (94.44)	1 (5.56)	
TB	240 (96.39)	9 (3.61)	
Other	142 (95.30)	7(4.70)	

*Two-sample T test

and those of high SEC i.e. medical aid patients and H3 & private ward patients, compared to those in lower SECs. GS prevalence among inpatients was significantly lower at 7.3% compared to that among outpatients which was 9.6%.The highest prevalence of GS when classified by indication for USS was seen among patients being investigated for biliary pathology (26.8%) and the lowest prevalence was seen amongst patients being imaged for trauma or post surgical complications (0.6%).

3.3 The Ratio of Symptomatic to Asymptomatic Gallstones

The respective proportions of symptomatic and asymptomatic GS are shown in Figure 3.1. Among all the patients with GS, 93 (32.8%) were symptomatic and 180 (63.4%) were asymptomatic. The ratio of symptomatic to asymptomatic GS was 1:1.9 (See Figure 3.1). Information regarding gallstone symtomatology was unavailable in 11(3.9%) of patients.

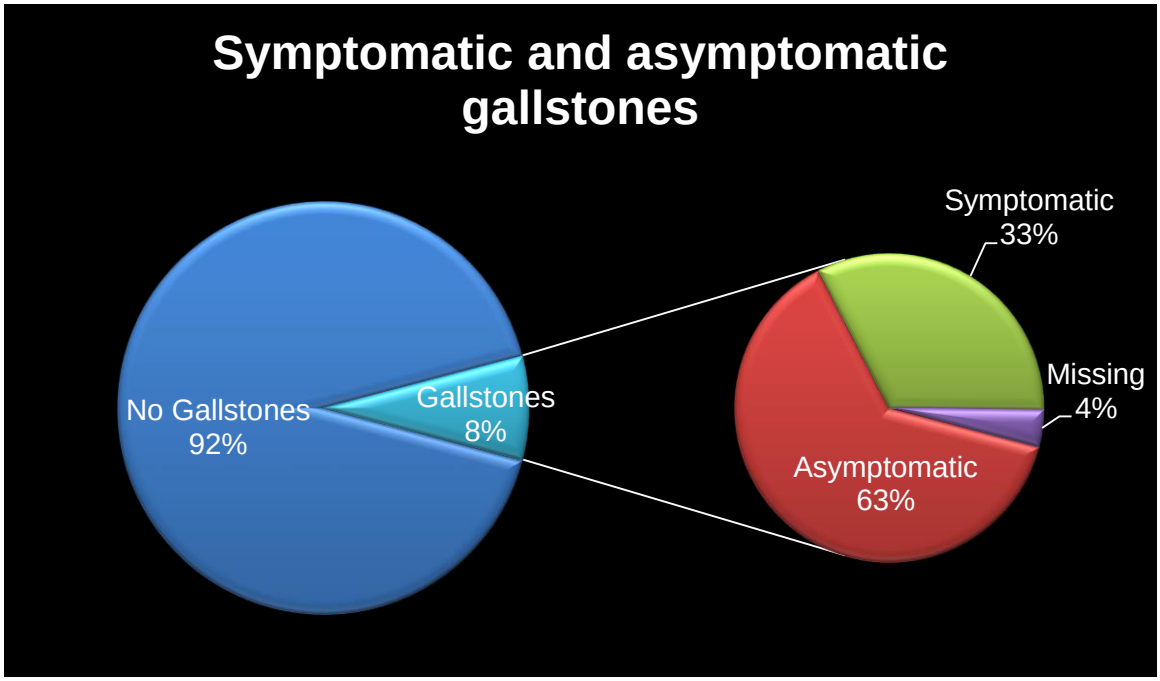

Figure 3.1: Symptomatic and asymptomatic gallstones

3.4 Correlation of clinical symptoms with ultrasound findings

Only a third of patients presenting with GS symptoms were confirmed to have GS on ultrasound. Symptoms in keeping with symptomatic GS were also observed in 11.65% of patients who did not have GS on ultrasound imaging. (See Table 4.3)The sensitivity of GS symptoms in correctly identifying those with GS on ultrasound was 34% while the specificity was 88%.The positive predictive value of GS symptoms was 19.9% and the negative predictive value was 93%.

Table 3.3: Correlation of clinical symptoms with ultrasound findings

	No gallstone symptoms N (%)	Gallstone symptoms N (%)	Missing N (%)	Total N (%)
No Gallstones	2 771(93.90)	374(80.09)	65(85.53)	3 210(91.87)
Gallstones	180(6.10)	93(19.91)	11(14.47)	284(8.13)
Total	2 951(100)	467(100),	76(100)	3 494(100)

Pearson Chi ^{2} p <0.001

Gallstone symptoms were frequently documented in patients being imaged for liver pathology (36.9%), abdominal pain, discomfort or tenderness (23.5%) and biliary pathology (26.2%). (See Table 3.4)

Table 3.4: Frequency of gallstone symptoms per ultrasound indication

Indication for ultrasound	Frequency of GS symptoms	Percentage
Malignancy work up	3	0.80
Trauma & Post surgical complications	3	0.80
Nephro-urogenital	5	1.34
Liver pathology	138	36.90
Abdominal pain/discomfort/tenderness	88	23.53
Gynaecological	2	0.53
Sepsis/Ascites	28	7.49
Biliary pathology	98	26.20
Other	2	0.53
Abdominal mass/distension/swelling/hernia	2	0.53

Pancreatic pathology	5	1.34
Total	374	100

3.4 Complications of gallstones

The majority of GS patients [266 (93.7%)] had no complications. Complications were seen in 6.3% of all GS cases. Complications were seen in 19.35% of patients who had symptomatic GS.

There were various complications of GS seen in the study which are shown in Figure 3.2. The most commonly observed complication was cholecystitis 11 (61.1%). Other complications noted were choledocholithiasis 3 (16.7%), pancreatitis 2 (11.1%) and cholangitis 2 (11.1%).

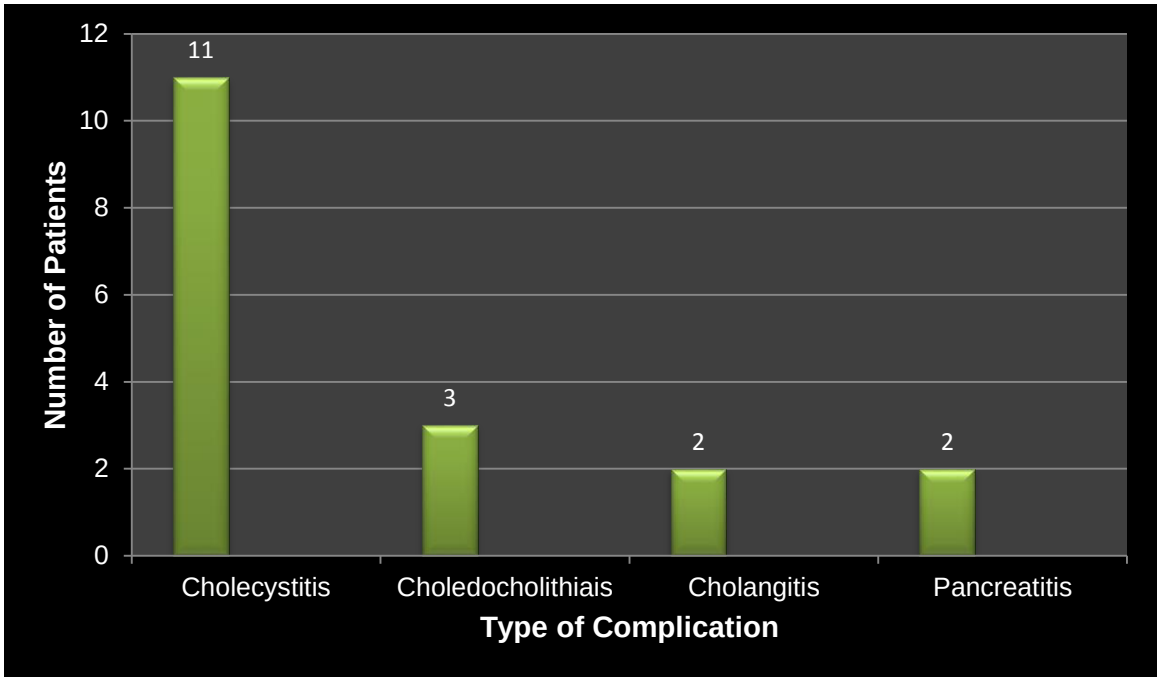

Figure 3.2: Types of gallstone complications observed in the study

3.5 Factors associated with gallstones

We explored the following factors for association with GS: gender, race, age, SEC and type of ward. Table 3.5 shows the unadjusted and adjusted logistic regression analysis. In unadjusted logistic regression, factors associated with GS were female gender [OR 1.97(1.51-2.56)], White race [OR 2.44(1.86-3.20)], Asian/Coloured race

[OR 2.12(1.40-3.22)], increasing age [OR 1.03(1.03-1.04)], H0 & emergency patients [OR 2.04(1.48-2.82)], H3 & private ward [OR 2.08(1.15-3.77), medical aid patients [OR 2.12 (1.50-2.99) and inpatients [OR0.73(0.57-0.94)].

In adjusted analysis, ward and SEC were no longer significantly associated with GS. Female gender [OR 1.87(1.42-2.46)], White race [OR 1.40(1.01- 1.93)] and increasing age [OR 1.03(1.02-1.04)] were significantly associated with GS.

Table 3.5: Factors associated with gallstones

Factor	Unadjusted logistic regression OR (95% CI) P Value	Adjusted logistic regression OR (95% CI) P Value
Gender		
Male	1	1
Female	1.97 (1.51–2.56) <0.001	1.87 (1.42-2.46) <0.001
Race		
Black	1	1
White	2.44 (1.86-3.20) <0.001	1.40 (1.01-1.93) 0.041
Asian/Coloured	2.12 (1.40-3.22) <0.001	1.52 (0.99-2.34) 0.058
Age	1.03 (1.03-1.04)<0.001	1.03 (1.02-1.04) <0.001
Socioeconomic class(SEC)	1	1
H1(low SEC)	2.04 (1.48-2.82) <0.001	1.04 (0.73-1.50) 0.822
H0& Emergency	1.07 (0.74-1.55) 0.715	1.21 (0.82-1.77) 0.333
patients	2.08 (1.15-3.77) 0.015	1.38 (0.74-2.60) 0.313
H2(Medium SEC)	2.12 (1.50-2.99) <0.001	1.23 (0.82-1.85) 0.324
H3 & Private ward		
Medical aid patients		
Ward		
Outpatients	1	1
Inpatients	0.73 (0.57-0.94) 0.013	0.81 k(0.62-1.06) 0.120

Chapter 4: Discussion

Introduction

This study was a retrospective cross sectional analysis of USS reports which aimed to describe the demographic, clinical and sonographic features of GS occurring in adult patients undergoing abdominal ultrasonography in the radiology department at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The study specifically looked at GS prevalence, symptoms and complications of GS as well as risk factors for developing GS in our study population.

The findings of the study are discussed below according to the suggested structure for discussion of scientific papers by Docherty and Smith (153). The discussion will be structured as: statement of principal findings, findings in relation to other studies and finally strengths and limitations of the study in relation to other studies.

4.1 Principal Findings

We conducted a retrospective cross sectional analysis of 3 494 abdominal ultrasound scan reports from 2009 and found that 284 (8.1%) had GS. The prevalence of GS was 10.2% and 5.5% among females and males respectively, with a female: male ratio of 2:1. The prevalence of GS among Whites, Coloureds, Asians and Blacks was 13.7%, 12.5%, 11.9% and 6.1% respectively. The ratio of symptomatic to asymptomatic GS was 1:1.9. The sensitivity and specificity of GS symptoms in correctly identifying those with GS on ultrasound was 34% and 88% respectively. The positive predictive value of GS symptoms was 19.9% and the negative predictive value was 93%.

The prevalence of GS complications among those with GS was 6.3% with the commonest observed complication being cholecystitis 11 (61.1%). Independent risk factors for GS were female gender [OR 1.97(1.51-2.56)], increasing age [OR 1.03(1.02-1.04)] and white race [OR 2.44(1.86-3.20)].

4.2 Findings in relation to other studies.

4.2.1 Study sample characteristics

The majority of patients in our study were black. This is a reflection of the general demographics of South Africa as 79.2% of the South African population is black(105). Our mean age was very similar to the Ghanaian study which had a mean

age of 47 (+/-18) years. Our study had more females than males which was similar to other studies (123,124,131,136,138,139).

Half of our patients were in a low SEC i.e. H1. This is a reflection of the South African demographics as shown in a report by Statistics South Africa and the National Treasury. This report stated that 55% of South Africans were below the 2006 indigence line of R2 400 per household per month(154).This is comparably similar to the H1 SEC classification used in this study. (See appendix 3) This finding may however not be similar to the private hospital patient profile as our study was conducted in a public institution. Our study had a higher proportion of pensioners compared to the national average of 6.5% which would be found in the general population (105). Pensioners are more likely to seek medical care due to age, and probably for financial reasons they are more likely to attend a public health care facility.

More than half of our study subjects were inpatients. This study was carried out at a tertiary referral institution where patients admitted there are likely to be complicated and needing multiple investigations including abdominal USS. No distinction in hospital admission status of patients was made in other hospital based studies (137–139,145,155,156).

The most frequent indication for abdominal USS in our study was in patients being investigated for malignancy. This is probably because USS is the most readily available radiological imaging to look for occult malignancy at CMJAH. This was different from data from Ethiopia and India which saw the highest number of investigations being requested for renal disease and pregnancy respectively (139,157).

4.2.2 Overall prevalence of gallstones

The overall prevalence of GS in our study of 8.1% was much lower than the general prevalence of GS in the western populations particularly in studies done in North America and Europe which showed prevalence rates of 10% -15% and 5.9% -21.9% respectively (12,119). Our prevalence however was higher than that of < 5% described for sub-Saharan Africa by other authors (11,12). This difference might arise from the fact that this earlier data was based on population studies done on

very small numbers in populations that were not comparable with the South African population such as the Masaai tribe (134,135).The Masaai are a nomadic tribe who live a predominantly active, rural life and are not exposed to urbanisation, obesity, high dietary fat and a sedentary lifestyle unlike the modern South African population (108–112,116,134). Therefore the non existence of GS among the Masaai cannot be generalised to all African populations.

The overall prevalence in our study is higher when compared to other recent population based African studies namely Sudan and Tunisia which have GS prevalence of 5.2% and 4% respectively (135,136). It is possible that the higher prevalence seen could be as a result of our study being hospital based compared to community based studies. Our study had higher prevalence compared to other hospital based surveys in Africa, namely Ethiopia and Ghana which showed GS prevalence of 5.2% and 5.9% respectively% (138,139). Our study however had a lower prevalence compared to that of 17.5% noted among Nigerian diabetic patients (145). The Nigerian study was conducted amongst a select high risk population of diabetic patients hence the higher prevalence observed. Our prevalence was lower than that observed in two hospital based Indian studies which had prevalence of 11.1% and 29.7% (156,157).

4.2.3 Gallstone prevalence in relation to gender

The GS prevalence among females in our study was similar to that seen among females in the Soweto study (140). The higher ratio of females with GS in our study was expected as females have a higher risk of developing GS compared to males (12). Conversely the studies in Ethiopia and Sudan showed a male: female ratio of 1:1. This may explain why our study has a higher overall GS prevalence than seen in Ethiopia and Sudan as we had a higher number of females with GS. Another explanation for the equal prevalence of GS among males and females in these studies could be the low level of exposure to hormonal contraception of women in these countries. Only 4.8% of women in Sudan and 13.2% in Ethiopia are exposed to hormonal contraception compared to 39.4% in South Africa. (158) Use of hormonal contraception and hormone replacement therapy (HRT) is associated with increased risk of developing GS (11,12,73,159). Some Asian studies also showed significantly higher GS prevalence in males compared to females while others showed no significant difference in male and female prevalence (42,61,126,141).

This may result from them having more of pigment than cholesterol GS (11,127). Pigment stones may not show the same relationship with gender as do cholesterol stones since pigment stones are not influenced by factors such as endogenous sex hormones, pregnancy, parity, OCP and HRT. We however were unable to type GS in our study in order to accurately compare with other studies whether GS subtype had any influence on gender prevalence.

4.2.4 Gallstone prevalence in relation to race

Prevalence of GS was highest among Whites and least among Black individuals. These results when compared to American data are similar in that American Blacks have the lowest GS prevalence as well (12). They are however dissimilar in that American Indians tend to have the highest prevalence of GS amongst all American races unlike the population in South Africa (12).The different genetic makeup of American and South African racial groups does not allow for accurate comparison between them. There is no literature that explores race in gallstone disease on the African continent. There is a possibility that the existing data on African GS surveys is based on studies carried out in populations that are less racially diverse. Our study was hospital based and this may explain the difference between our findings and American data.

4.2.5 Gallstone prevalence in relation to patient hospital status

More outpatients had GS compared to inpatients. This is likely due to the fact that most GS remain asymptomatic, negating the need for admission to hospital (90,160). Hence the finding of a higher GS prevalence among outpatients compared to inpatients.

4.2.6 Gallstone prevalence in relation to SEC

Higher GS prevalence was noted in pensioners and in those of higher SEC. Pensioners being older individuals have a higher risk of GS compared to younger individuals. They are more likely to be female as well as there are more females than males over the age of 65 in South Africa (105).Female gender increases GS risk. This further increases the GS risk among pensioners. Those in the higher SECs are likely to be more urbanised and consume a more westernised diet hence putting

them at risk of developing GS. This finding was also described in other studies (129,130).

However some work done in the USA showed an inverse relationship between SEC and GS prevalence (148). Variations in methods used to define SEC may account for this discrepancy in findings. The American study used four measures of SEC i.e. occupation, education, income and residential neighbourhood whereas ours only used income or assets. The Ethiopian study used rural and urban dwelling as SEC, but a comparison of these two groups was not made available in their results (139). The study in Xinjiang, China used the regional economy of the study site as SEC and compared it to findings from regions in China with different economies and showed that GS were commoner in lower SEC regions (127). An Indian study of 1 695 adults used a modified Kuppuswamy's classification for SEC, which is based on occupation, education, and monthly income. Their results failed to show a difference in GS prevalence among all SECs in this study (161). We were also unable to find a statistically significant association between SEC and GS.

In our study there were fewer patients in the higher SECs hence any patients with GS in these classes were likely to reflect a higher prevalence. For example out of only 5 H3 patients in the study, one had GS resulting in a GS prevalence of 20% among H3 patients. This being a public institution based study we may not have accurately represented higher SEC patients as they are more likely to afford private health care and thus not be included in our study.

4.2.7 Gallstone prevalence in relation to indication for ultrasound

The highest prevalence of GS was seen in patients undergoing USS for biliary pathology. This was expected as gallstones form in the biliary system and symptoms they give rise to, are consistent with biliary disease and were more likely to be documented as such by the requesting physician. This is different from a hospital based study in India where most GS were seen among pregnant women (157). This could have resulted from pregnant women constituting the largest proportion of their sample (28.3%) and also from the fact that pregnancy is a risk factor for GS.

4.2.8 Ratio of Symptomatic to Asymptomatic Gallstones

As expected the prevalence of GS related symptoms among those who had GS was higher than that of 10-20% described in the population based natural history of GS

(160). The ratio of symptomatic to asymptomatic GS of 1:1.9 in our study was different from that of 1:1 seen in another hospital based study in Ethiopia (139). However data from both our study and the Ethiopian study showed higher proportions of symptomatic GS than in population based studies (129,130,162).This discrepancy in results may arise from bias introduced by hospital based studies which are more likely to include more symptomatic patients than would community based studies. A community based study in Argentina however showed that just over half of the patients with GS in Buenos Aires were symptomatic (123).This result is unusual for a community based study as most GS are expected to be asymptomatic (11,160).

The sensitivity of GS symptoms in correctly identifying those who had gallstones was very low as a sizeable proportion of patients without GS had matching symptoms. This was probably because symptoms arising from other abdominal organs such as the liver can mimic symptomatic GS. This is further supported by the fact that patients being imaged for liver disease and those who presented with non specific abdominal pain, discomfort or tenderness constituted 37% and 24% respectively of all patients who were classified as symptomatic GS.

A study in Peru that was comparing high and low altitude dwelling populations concluded that abdominal pain was a poor indicator of GS as it was equally prevalent between those who had GS and those who did not have GS (122). Safer *et al* showed that typical biliary pain had a specificity of 97.6% which was much higher than ours of 88%(136). Theirs being a prospective study was probably able to uniformly interview patients with minimal subjectivity.

In a Danish study of 3 608 adults, the positive predictive values of abdominal symptoms ranged from 0% to 25.0% while the negative predictive value ranged from 93.2% to 94.2% (143). These findings were similar to our findings of 34% positive predictive value and 93% negative predictive value. These findings reinforce the unreliability of clinical symptoms alone in correctly identifying patients with symptomatic GS.

4.2.9 Complications of Gallstones

Prevalence of gallstone complications in our study was higher than 0.2% which was seen among pregnant women in Nigeria. Our findings however were much lower

than that of 22.1% seen in the Ethiopian hospital based survey (139). Cholecystitis was our commonest complication as in other studies, however in Ethiopia their commonest complication was choledocholithiasis (137,139).Perhaps this could result from GS in Ethiopian patients primarily forming in the bile ducts as opposed to the gallbladder suggestive of pigment stones, however this subject was not addressed in their study.

As our study was done retrospectively, we may have missed complications that are better diagnosed clinically e.g. cholangitis and this may account for the lower complication prevalence observed in our study when compared to other hospital based studies (3,139,163). The prevalence of complications observed among patients with symptomatic GS in our study was 19.4% compared to 5.8% found at a referral hospital in India (156). Almost all complicating GS are preceded by one or more episodes of biliary symptoms (164).

4.2.10 Factors Associated with Gallstones

The statistically significant association between female gender and GS is well established in literature (11,12,136,138,159). Studies conducted in Iran showed very low GS prevalence of 0.8%-1.8% (132,133). Women were under-represented in these study samples due to cultural practices yet there was a statistically significant association between female gender and GS. The strong association between female gender and GS may be related to female reproductive hormones, use of the hormonal contraception, HRT or parity, however this study was not specifically designed to investigate these risk factors (12,27,165).

Some studies however have shown different results. In a Japanese survey of 2 584 volunteers from the Okinawa community, the overall GS prevalence was 3.2% with 4.0% for females and 2.5% for males. The risk factors for GS in this study were increasing age and fatty liver on ultrasound. There was no statistically significant association between GS and female gender (125). In a Chinese study comparing the Han and the Uinghur ethinic groups, female gender was a significant GS risk factor in the Uinghur ethnic group only (127). The Uinghur group were more westernised in their diet and developed cholesterol GS as opposed to the Han group who developed mostly pigment stones (127). Female gender may be a risk factor for

developing cholesterol GS and not pigment stones which have a different pathophysiology. However more research is needed to confirm this.

Our study also showed a statistically significant association between White race and GS, this is similar to findings in the United States that show that White Americans had a higher GS prevalence than Black Americans (12). There may be underlying race specific genetic variations in genes responsible for bile and cholesterol metabolism pathways that result in varying GS prevalence among different racial groups.

The association between increasing age and GS noted in our study is also similar to other previous studies (11,136,138,145). It has been proposed that aging increases length of exposure to GS risk factors (166).

4.3 Strengths of the study in relation to other studies

We included both males and females. This is in contrast to other studies that primarily focused on specific populations such as elderly women, pregnant women and diabetics (137,140,145). This eliminated bias that may arise from studying only one specific group of individuals e.g. females only as it is known that female gender is associated with a higher risk of developing GS (11,12).

This study involved all the population groups (races) that are formally recognised in South Africa i.e. Blacks, Whites, Asians and Coloureds (105). This is comparable with the North and South American surveys which documented the differences in GS prevalence among different races and ethnic groups (118,167).There are no other studies on the African continent that investigated racial differences in GS prevalence and our study seems to be the only study conducted in Africa that explored this issue.

Our study included all ages above 18 years. This is in contrast to the Soweto study which specifically recruited elderly women with an age range of 55-85 years old and the Taiwanese study which concentrated on only the elderly in a rural community (140,166). As increasing age is a risk factor for GS, studies with a higher mean age may result is a higher prevalence of GS (11). The French study excluded individuals under 30 years of age due to poor study compliance as a result their results do not

accurately represent the entire French adult population specifically the younger adults (142).

Our study explored SEC of patients using personal or household income and assets. Socio-economic classification was not explored in most of the studies done in Africa. The study done in Ethiopia classified patients into rural and urban dwellers based on their addresses and used this as SEC (139). This may not be an accurate way of assessing SEC as the study did not consider personal or family income/assets as was done in our study.

4.4 Limitations of the study in relation to other studies

Our study as with most other retrospective record reviews was prone to effects of confounding, missing and incorrect data. The electronic 'medicom' data capturing system was vital in capturing data that was not initially available on the USS reports. However the medicom system classified patients who were referred to the CMJAH radiology department for USS from smaller health care centres as outpatients. This is despite the fact that some of these patients were actually admitted at these referring health care centres and may not be comparable to mobile and clinically stable outpatients coming for USS from CMJAH outpatient clinics with whom they were put in the same category.

The USS reports were hand written and in certain instances the indication for the investigation was illegible or the request form was missing this resulted in the inability of the investigators to accurately classify GS as either symptomatic or asymptomatic. As a result information pertaining to symptomatology of GS was missing in 4% of our GS patients.

Classification of GS into either symptomatic or asymptomatic was based on the information provided by the USS requesting doctor. Not all doctors provided all the relevant patient information on the requesting forms and this may have misled USS report interpretation. The ultrasound request form is not filled in any systematic way. As a result there were over 60 USS indications that had to be grouped into similar groups to allow for data analysis. Grouping of indications may have introduced bias.

The collection of symptoms used in the study to define GS symptoms is not specific to GS disease alone and can arise from other abdominal organs. As a result the

sensitivity and positive predictive value of symptom based diagnosis of GS were very low in this study. The CMJAH socio-economic classification is based on patient self reported income and salary slips where ever possible. It is vulnerable to inaccuracy as patients may misrepresent themselves in order to qualify for a lower fee paying or non paying SEC category. This may explain why there was no significant relationship between SEC and GS.

It was not possible to exclude previously symptomatic GS patients who may now have had a scan for an indication that was unrelated to their GS. This may have resulted in them being misclassified as asymptomatic. This is in contrast to other studies that were done prospectively and were spared from these challenges (136,137,145).

It is worth noting that obstetric ultrasounds at CMJAH are done in a separate dedicated obstetric unit and that data was therefore not captured in this study, this resulted in the exclusion of a known high risk group from the study. Our study, unlike work done prospectively in Nigeria and Tunisia was not able to assess other possible GS risk factors such as BMI, cholesterol levels or exposure to hormonal contraception (136,137,145).

The diagnosis of GS complications in this study was limited to those described by the sonographer. This study may therefore have missed some complications of GS that are more accurately diagnosed clinically such as cholangitis, as outlined in the Tokyo guidelines (3,163). There were instances were sonographers could not state with certainty whether GS were present or absent, these cases were classified as absent GS. This may have missed some GS which may have needed an alternative imaging modality to be more readily visualised.

Our study was conducted at a tertiary referral hospital where complicated and gravely ill patients are often referred for specialist assessment and intervention. This may have resulted in our study sample including more patients with symptomatic and complicated GS than would be found in the community or at primary and secondary health care centres.

This being a hospital based study may have overestimated the true community based GS prevalence in South Africa. This is in contrast to community based studies

such as that done by Safer *et al* (136).The findings of our study are therefore not generalisable to the general population but are useful in predicting prevalence of GS in public hospital populations in South Africa.

Our study was unable to explore the types of GS among our patients as was done in another study (127). The prevalent risk factors in the South African population would favour the development of cholesterol GS but we were unable to investigate this. The data from this study is from a public hospital and it is likely that findings from a private institution may show different results to ours.

Chapter 5: Conclusions and Recommendations

Introduction

This chapter discusses the meaning and implication of the study. It also addresses recommendations for clinicians and policy makers as well as highlights areas of possible future research in relation to this subject.

5.1 Conclusions

The overall prevalence of GS in this study was higher than that of less than 5% previously for Sub-Saharan Africa in literature (11,12). The prevalence of complications among all who had GS was 6.3% which was lower than that described in an Ethiopian hospital based study (139). Complications among those who had symptomatic GS was higher than our overall complication prevalence at 19.4%. The sensitivity and positive predictive value of GS symptoms in correctly identifying those with GS were low. This shows that clinical symptoms alone are an unreliable identifier of patients with symptomatic GS. Risk factors for GS were female gender, increasing age and white race. Race is an important but unexplored risk factor for GS in African populations. It is possible that the increasing urbanisation, obesity, metabolic syndrome and sedentary lifestyle may be resulting in a higher prevalence of GS among South Africans than was previously described for Sub-Saharan Africa.

5.2 Recommendations

In view of our findings, health care workers should be trained to promptly recognise clinical symptoms of symptomatic or complicated GS and have a high index of suspicion in older females of white race. Clinical symptoms alone cannot be relied upon to accurately identify patients with GS as similar symptoms commonly occur in patients without GS. Ultrasound services should be readily available as USS can readily confirm the presence or absence of this common digestive disorder.

Our specialist training programme will need to ensure that all our graduating health care workers particularly general surgeons are confident in management of GS disease as this is a common disease. Policies which encourage implementation of public health education of the South African population on a healthier lifestyle (healthier diet, weight loss programmes and exercise etc) may result in a decrease in GS prevalence ultimately saving the health system some money.

Digitalisation of the radiology department will enable electronic documentation, capturing and storage of USS reports in a non ambiguous format that will allow correct interpretation of data by all who need access to it for clinical care of patients as well as research. It will also prevent loss of data that may occur if data is stored as hard copy reports. A systemised structured ultrasound request form would make it more accurate to collect data for research.

In view of the fact that this was a hospital based study, a community based prospective study is recommended to more accurately ascertain the true prevalence of GS in the South African general population. A private institution based study would also be useful to compare our findings. The impact of obesity, sedentary lifestyle, dyslipidaemia and the metabolic syndrome on the prevalence and type of GS in South Africa should also be investigated.

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Appendices

APPENDIX 1: Sample Size Calculation

In this calculation the following assumptions were made:

α = 0.05 (two-sided)

Power = 0.9

Null hypothesis: p=0.052 (The prevalence of ultrasound diagnosed GS in patients who have had an ultrasound at a hospital in Ethiopia was found to be 5.2%.

Alternative hypothesis: p (postulated prevalence) = 0.1 (We expect the prevalence to be higher in urban Johannesburg given the westernised lifestyle and obesity).

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. sampsi 0.052 0.1, power(0.9) onesample

Estimated sample size for one-sample comparison of proportion
  to hypothesized value

Test Ho: p = 0.0520, where p is the proportion in the population

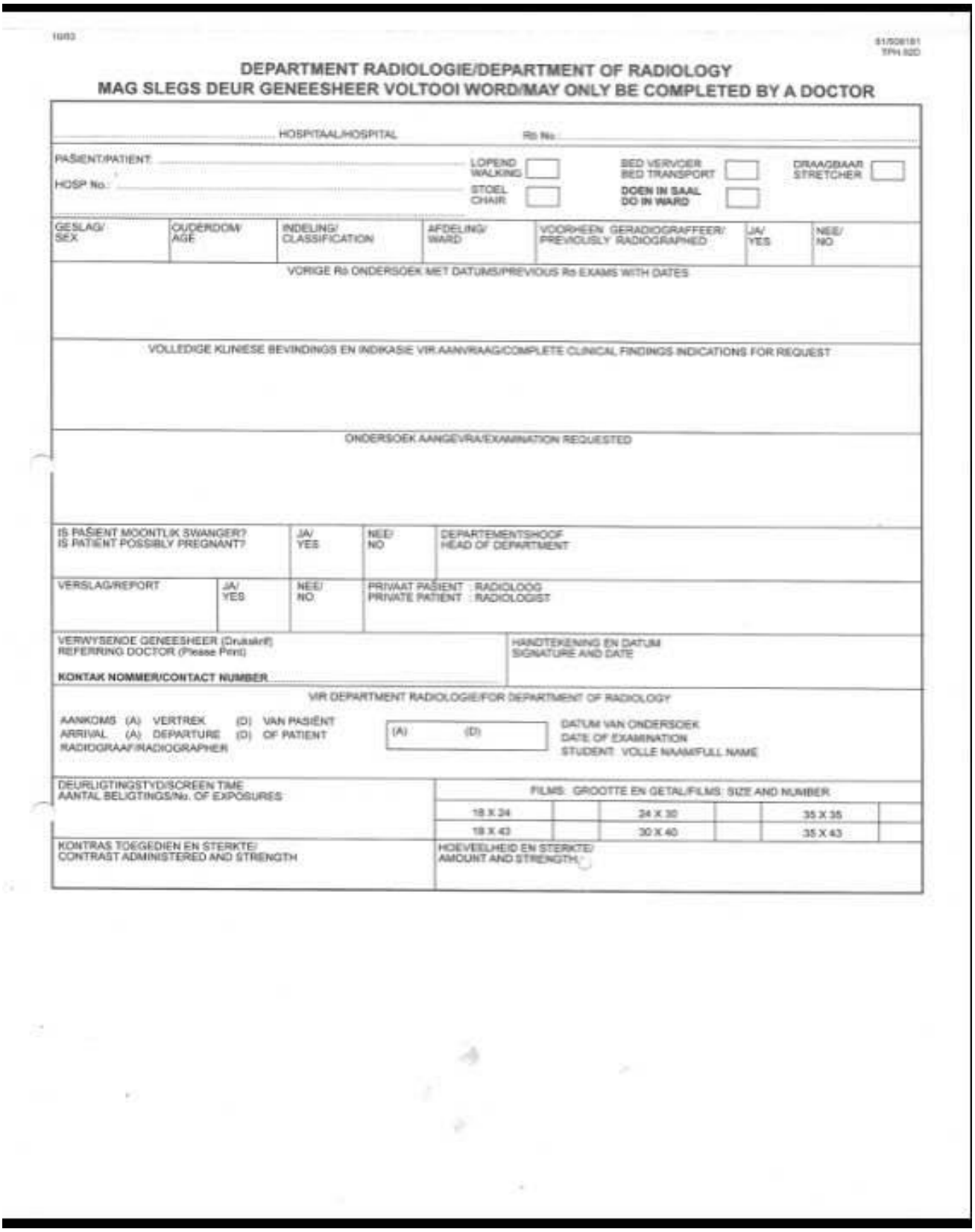
Assumptions:

        alpha =   0.0500  (two-sided)
        power =   0.9000
 alternative p =   0.1000

Estimated required sample size:

            n =      292
```

APPENDIX 2: Ultrasound scan request form



DEPARTMENT RADIOLOGIE/DEPARTMENT OF RADIOLOGY
MAG SLEGS DEUR GENEESHEER VOLTOOI WORD/MAY ONLY BE COMPLETED BY A DOCTOR

HOSPITAAL/HOSPITAL — Rtn No:

PASIENT/PATIENT: — LOPEND/WALKING ☐ — BED VERVOER/BED TRANSPORT ☐ — DRAAGBAAR/STRETCHER ☐
HOSP No.: — STOEL/CHAIR ☐ — DOEN IN SAAL/DO IN WARD ☐

GESLAG/SEX	OUDERDOM/AGE	INDELING/CLASSIFICATION	AFDELING/WARD	VOORHEEN GERADIOGRAFFEER/PREVIOUSLY RADIOGRAPHED	JA/YES	NEE/NO

VORIGE Rs ONDERSOEK MET DATUMS/PREVIOUS Rs EXAMS WITH DATES

VOLLEDIGE KLINIESE BEVINDINGS EN INDIKASIE VIR AANVRAAG/COMPLETE CLINICAL FINDINGS INDICATIONS FOR REQUEST

ONDERSOEK AANGEVRA/EXAMINATION REQUESTED

IS PASIENT MOONTLIK SWANGER? IS PATIENT POSSIBLY PREGNANT?	JA/YES	NEE/NO	DEPARTEMENTSHOOF HEAD OF DEPARTMENT

VERSLAG/REPORT	JA/YES	NEE/NO	PRIVAAT PASIENT : RADIOLOOG PRIVATE PATIENT : RADIOLOGIST

VERWYSENDE GENEESHEER (Drukskrif)
REFERRING DOCTOR (Please Print) — HANDTEKENING EN DATUM / SIGNATURE AND DATE

KONTAK NOMMER/CONTACT NUMBER

VIR DEPARTMENT RADIOLOGIE/FOR DEPARTMENT OF RADIOLOGY

AANKOMS (A) VERTREK (D) VAN PASIËNT
ARRIVAL (A) DEPARTURE (D) OF PATIENT
RADIOGRAAF/RADIOGRAPHER — (A) (D)

DATUM VAN ONDERSOEK
DATE OF EXAMINATION
STUDENT VOLLE NAAM/FULL NAME

DEURLIGTINGSTYD/SCREEN TIME
AANTAL BELIGTINGS/No. OF EXPOSURES

FILMS: GROOTTE EN GETAL/FILMS: SIZE AND NUMBER

18 X 24		24 X 30		35 X 35	
18 X 43		30 X 40		35 X 43	

KONTRAS TOEGEDIEN EN STERKTE/
CONTRAST ADMINISTERED AND STRENGTH

HOEVEELHEID EN STERKTE/
AMOUNT AND STRENGTH

APPENDIX 3: Socio-economic Classification

JOHANNESBURG HOSPITAL

CLASSIFICATION AND TARRIF CATEGORIES BASED ON INCOME AND STATUS
AS FROM 1/1/2006

OUT-PATIENTS (CLINICS)

NB: ALL FINANCIAL CATEGORIES ARE NOW FULLY UPFS RATES

FINANCIAL CLASSIFICATION CODES FOR COMPUTER

COMPUTER CODE	INCOME/ASSETS FOR INDIVIDUAL	INCOME/ASSETS FOR FAMILY UNIT	TARRIFS CLINICS
H0	FORMALLY UNEMPLOYED SOCIAL PENSIONER		FREE
H1	Annual income less than R36 000 Assets less than R151 200	Annual income less than R50 000 Assets less than R231 300	R40
H2	Annual income R36 000 - R72 0000 Assets for R151 200 – R321 200	Annual income R50 000 – R100 000 Assets not more than R231 300 – R473 300	R120
H3	Annual income R72 000 and more or Assets worth more than R321 200	Annual income R100 000 and more or Assets worth more than R473 300	R172
PM	1. A member of a medical scheme 2. Prisoners awaiting trial 3. Prisoners already sentenced		R172
H2	An applicant where income/information is not readily available		R120
HD	SADF Members – Must have DD63- if not be classified according to income. Defence Force requires that the original pink copy of the DD 2703 be forwarded to the Accounts Department.		UPFS(Bills to be raised by Patient Accounts)
PP	Foreign patients (Exclusively for medical treatment, visitors or emergencies) Permission from clinical executive must be obtained. Deposit/guarantee must be obtained. An applicant as identified in regulation 4(2) Refusing to give income – provisional classification [Hospital patient on request to be treated by a private practitioner].		R172

Free codes

U6	Children under 6 (Excluding medical aid patients)
HG	All hospital patients that are exempted from paying
WC	Injury on duty – see foot note
PG	Private patients
CC	Committed children
SW	SW – Injury on duty- Staff

APPENDIX 4: Data collection sheet

DEMOGRAPHIC INFORMATION

Study Number : _____ Date of imaging : _____

Age : _____ Ward : _____

Sex : Male ☐ Female ☐

Race : Black ☐ White ☐ Asian ☐ Other specify :____

Patient Class : H_0 ☐ H_1 ☐ H_2 ☐ H_3 ☐ Other specify :____

*Please see appendix 2

INDICATION FOR SONAR

☐ Related to gallstones ☐ Not related to gallstones

Specify:_____ Specify: _____

(*epigastric or right upper quadrant pain(+/- jaundice) or a positive Murphy's sign, or if the requesting physician suspected gallstones

SONAR FINDINGS

☐ Gall bladder seen ☐ Gall bladder not seen

☐ Cholecystectomy

☐ Other Specify _____

Gall stones : ☐ Present ☐ Absent

Gall stones site : ☐ Gall bladder ☐ Biliary tree

Number of gall stones : ☐ Single ☐ Multiple

COMPLICATIONS OF GALLSTONES ON SONAR

☐ Cholecystitis ☐ Cholangitis

☐ Pancreatitis ☐ Choledocholithiasis

☐ Other specify : _____

APPENDIX 5: Ethics Clearance Certificate

R14/49 Dr Tarisai Sharon Nyahoda

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140230

NAME: (Principal Investigator)	Dr Tarisai Sharon Nyahoda
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Glance at Gallstones in South Africa: A Two Year Review of Sonographic Findings at a Tertiary Hospital
DATE CONSIDERED:	28/02/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr A Mahomed
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	25/04/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

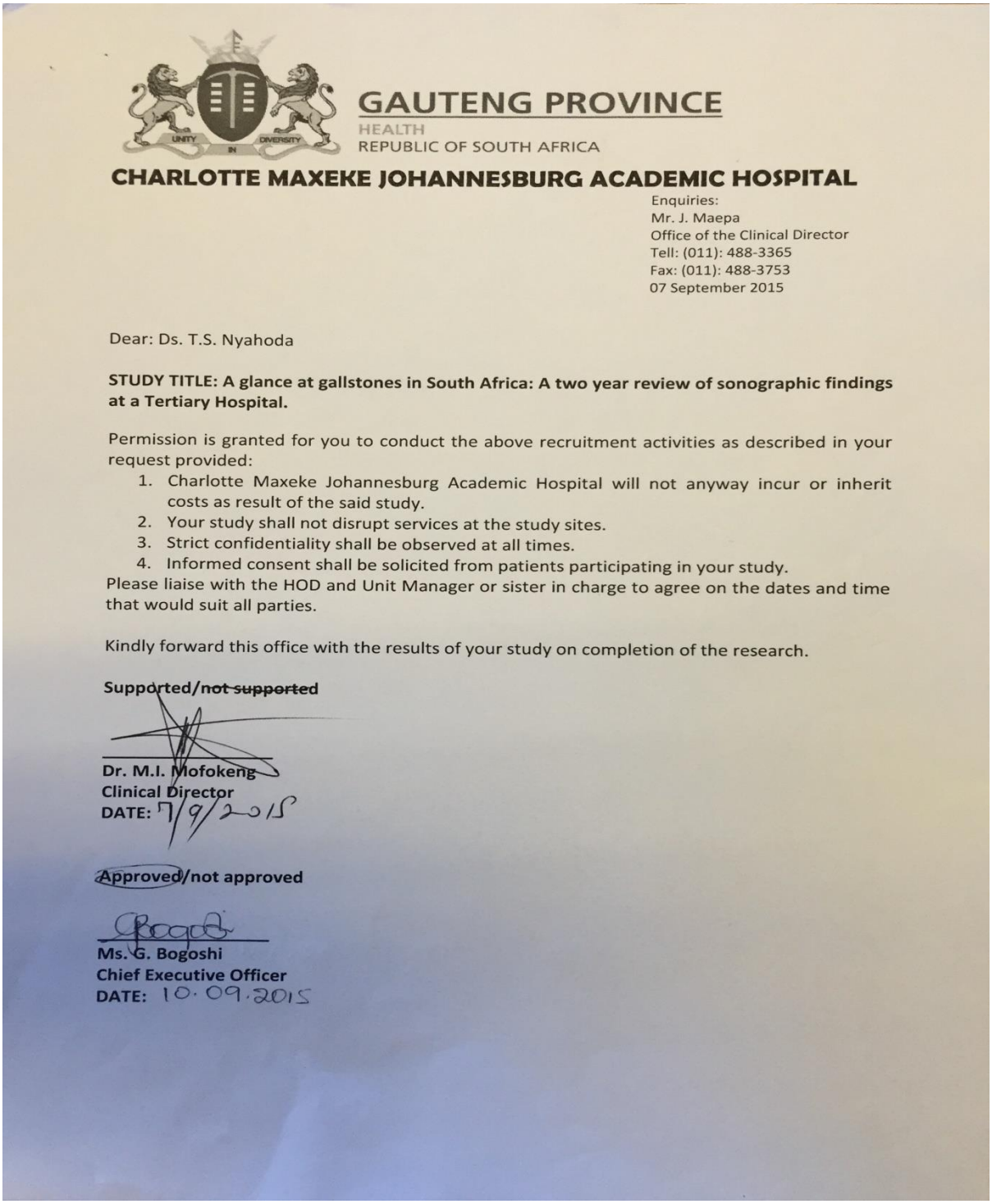
To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**

Principal Investigator Signature — Date: 6/6/2014

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 6: Letter of study approval



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011): 488-3365
Fax: (011): 488-3753
07 September 2015

Dear: Ds. T.S. Nyahoda

STUDY TITLE: A glance at gallstones in South Africa: A two year review of sonographic findings at a Tertiary Hospital.

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 7/9/2015

~~Approved~~/not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 10.09.2015

APPENDIX 7: Application for change of study title

Faculty of Health Sciences, Postgraduate Office
Phillip VTobias Building, 2nd Floor
Cnr York & Princess of Wales Terrace, Parktown 2193
Tel: (011) 717 2745 | Fax: (011) 717 2119
Email: Mathoto.senamela@wits.ac.za

APPLICATION FOR CHANGE OF TITLE OF APPROVED RESEARCH REPORT, DISSERTATION OR THESIS

Student Surname and Initials: NYAHODA T.S
Student Number: 308224
Degree: MMED
Department: Medicine (Gastroenterology)
Telephone: 0728403417
E-mail: tnyahoda@gmail.

Current Title: A glance at gallstones in South Africa: A 2 year review of sonographic findings at a tertiary hospital

New Title: A glance at gallstones in South Africa: A one year review of sonographic findings at a tertiary hospital

Motivation / Reason for title change:
The estimated required sample size for this study is 292. After collecting a years worth of data the number was already exceeding 3000. The Statistician felt that a years worth of data was enough to answer the research question and that there was no value in extending data collection over a two year period

Approvals / signatures:

Student Signature: Date: 18/03/15

Supervisor(s) names: Prof A.D Mahomed
Departments: Int. Medicine (Gastroenterology)
Supervisor(s) Telephone: 0834692802
Supervisor(s) E-mail: Adam.Mahomed@wits.ac.za
Supervisor 1 Signature:

Supervisor(s) names: Prof. V. Marpome Zulu
Departments: Diagnostic Radiology.
Supervisor(s) Telephone: 011 488 3368
Supervisor(s) E-mail: Victor.Marpome-zulu@wits.ac.za
Supervisor 2 Signature:

Supervisor(s) names: ALISON BENTLEY
Departments: FAMILY MEDICINE
Supervisor(s) Telephone: 074 236 3087
Supervisor(s) E-mail: dralisonbentley@gmail.com
Supervisor 3 Signature:

APPENDIX 8: Approval of change of study title

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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

Reference: Ms Thokozile Nhlapo
E-mail: thokozile.nhlapo@wits.ac.za

14 May 2015
Person No: 308224
TAA

Dr TS Nyahoda
PO Box 90
Wits University
Johannesburg
2050
South Africa

Dear Dr Nyahoda

Master of Medicine: Change of title of research

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Medicine** has been approved:

From:	**A glance at gallstones in South Africa: A 2 year review of sonographic findings at a tertiary hospital**
To:	**A glance at gallstones in South Africa: A one year review of sonographic findings at a tertiary hospital**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

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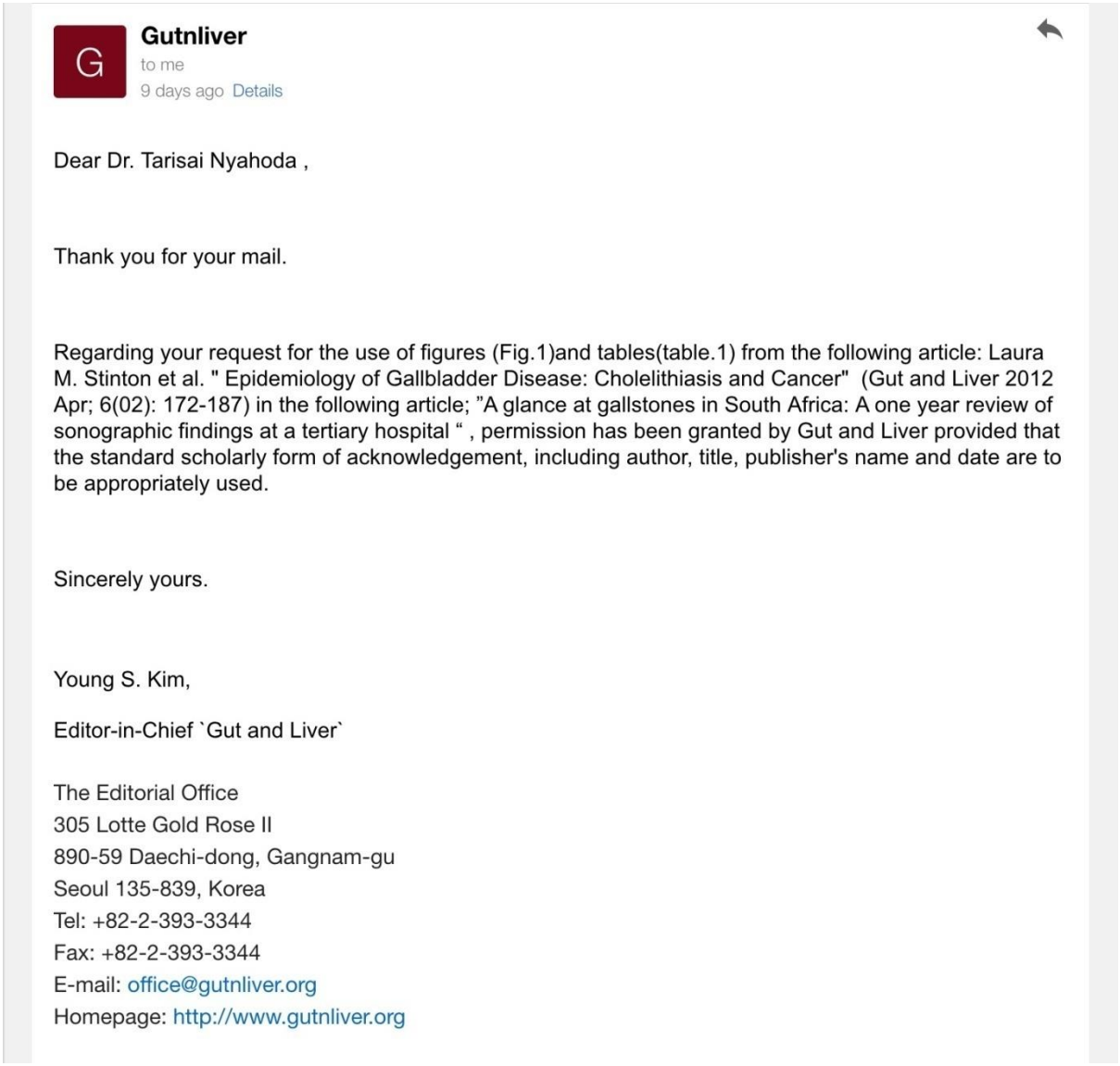

Gutnliver
to me
9 days ago Details

Dear Dr. Tarisai Nyahoda ,

Thank you for your mail.

Regarding your request for the use of figures (Fig.1)and tables(table.1) from the following article: Laura M. Stinton et al. " Epidemiology of Gallbladder Disease: Cholelithiasis and Cancer" (Gut and Liver 2012 Apr; 6(02): 172-187) in the following article; "A glance at gallstones in South Africa: A one year review of sonographic findings at a tertiary hospital " , permission has been granted by Gut and Liver provided that the standard scholarly form of acknowledgement, including author, title, publisher's name and date are to be appropriately used.

Sincerely yours.

Young S. Kim,

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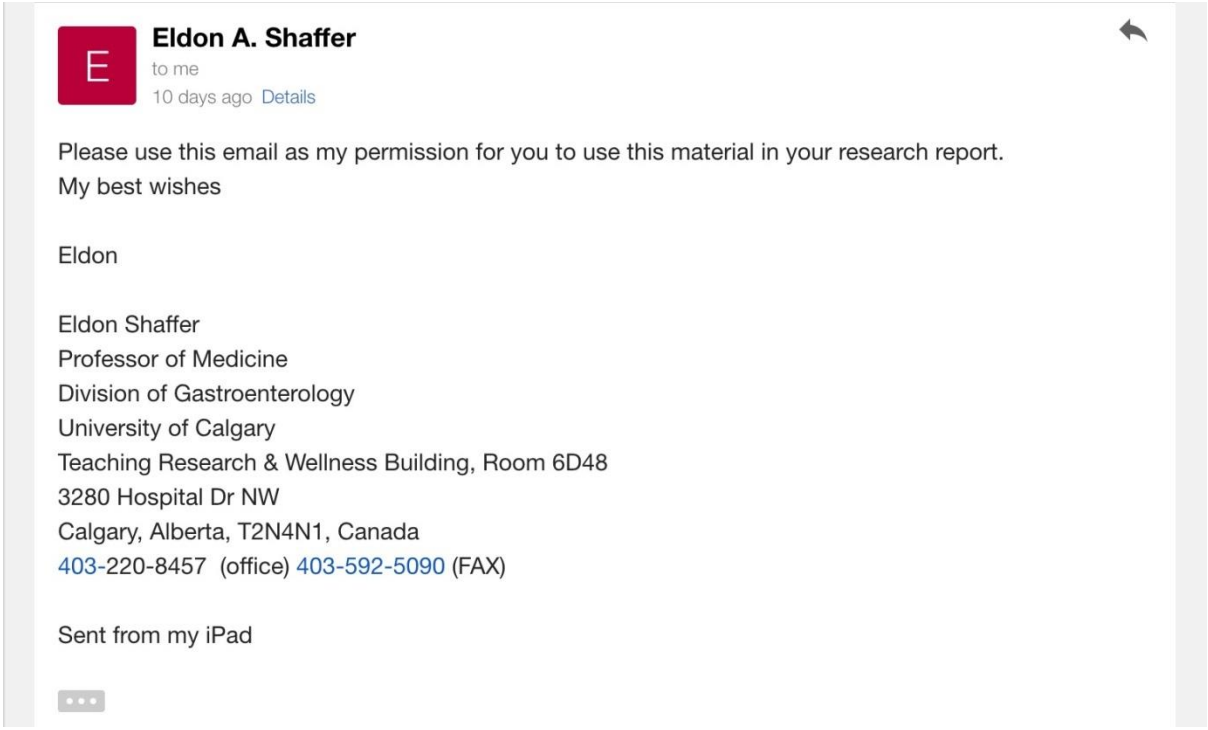

Eldon A. Shaffer
to me
10 days ago Details

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My best wishes

Eldon

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