

https://dspace.org/

Primary sclerosing cholangitis in a cohort of South African petients with inflammatory bowel disease at Charlotte Maxeke Johannesburg Academic Hospital

Alshmandi, Mohamed Almokhtar Mohamed

2018

https://hdl.handle.net/10539/25595

Downloaded from a DSpace repository. https://dspace.org/

PRIMARY SCLEROSING CHOLANGITIS IN A COHORT OF SOUTH AFRICAN PATIENTS WITH INFLAMMATORY BOWEL DISEASE AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Mohamed Almokhtar Mohamed Alshmandi

Student number: 871119

A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, in fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine.

Johannesburg, 2018

Declaration

I, Mohamed Alshmandi, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the clinical discipline of Internal Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.
Signature: Mohamed Alshmandi
5th day of June 2018.

Dedication

Dedicated to my family, colleagues and patients who have inspired my research.

Abstract

Background:

Primary Sclerosing Cholangitis (PSC) is a chronic, progressive cholestatic liver disease of unknown aetiology. PSC has a very strong association with Inflammatory Bowel Disease (IBD). The phenotype in patients with PSC alone can be different to that of patients with both PSC and IBD (PSC-IBD).

The incidence and prevalence of PSC varies considerably in Asian and Western studies.[1] The differences in the epidemiological data recorded suggest that the presentation of PSC may vary in different populations. There is a dearth of information on this topic from African countries in general and more specifically in the Black South African population.

Aim:

The aims of this study are to:
1- Describe the demography, clinical features, laboratory findings, radiographic imaging and outcome of subjects with PSC with a particular emphasis on the Black South African cohort.
2- Compare the findings in patients with isolated PSC to those with PSC-IBD.

Methods:

This study was a retrospective chart review of 305 patients with PSC and/or IBD. The study focused on patients with PSC and PSC-IBD. The patients were seen at the Gastroenterology clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a tertiary academic hospital affiliated to the University of the Witwatersrand in Johannesburg, South Africa. The study period extended from 1 January 2008 to 31 May

2014. The data was extracted using a structured data sheet (see Appendix A). The data was captured in Microsoft Excel and later exported into Statistical Product and Service Solutions (SPSS). Descriptive statistics were used to summarize the demographic data of the study cohort in general and separately for the Black African sub-group. The Chi-square test of association was used to assess whether there were any association between PSC and the following factors: gender; ethnicity and a history of smoking.

Results:

There were 69 patients with PSC. There was an almost equal distribution between females (51%) and males (49%). In females the age at diagnosis was marginally higher (42 years) than in males (39years).

The majority of the cohort was Black African (68%); the rest comprised Whites (15%); Asians (13%) and Coloureds (4%). The demography; clinical and radiological findings and outcomes in the Black African group were similar to the rest of the cohort. The one significant difference noted between the two groups was the frequency of liver cirrhosis which was more common in the other race groups.

There was an almost equivalent distribution between patients with PSC alone (49%) and those with PSC-IBD (51%). At initial presentation the majority of patients (60%) had features indicative of PSC; almost one quarter (26%) had IBD and the remainder of the patients had features of PSC-IBD. The demography; clinical and radiological findings was similar in patients with PSC when compared to those with PSC-IBD. The significant differences noted between the two groups were the higher detection rate of isolated common bile duct involvement in patients with PSC and the increased colonic involvement in patients with PSC and Ulcerative Colitis (UC).

Conclusions

In our setting patients with PSC, including specifically the Black African cohort have a similar profile in terms of demography, clinical, laboratory and imaging findings to previously described large cohorts in the western world.[1]

This study didn't reveal any association between the PSC or PSC-IBD and ethnicity or gender. The study showed that smoking conferred a protective effect against the development of PSC.

The data in this study supports the observations of other studies that colonic inflammation is important for PSC development particularly with ulcerative colitis. An underlying history of IBD and autoimmune disorders should be sought in patients with PSC.

Acknowledgements

I would like to thank my supervisors for their patience, support, guidance and enthusiasm during this time. I would like to acknowledge the staff at the National Health Laboratory Services (NHLS) and Radiology Department for their help during data collection, and the statistician who assisted me with data analysis.
I would like to acknowledge the patients at CMJAH who inspire me daily.

Table of contents

Content	***Page Number***
Title page	I
Declaration	II
Dedication	III
Abstract	IV-V
Conclusion	VI
Acknowledgements	VII
Table of contents	VIII-X
List of abbreviations	XI-XII
List of figures	XIII
List of tables	XIV-XV
Chapter One (Literature Review)	
1.0 Introduction	1
1.1 Definition	2-3
1.2 Epidemiology	2-3
1.3 Aetiology	3-5
1.4 Disease Presentations	5-6
1.5 Disease Complications	6-7
1.6 Disease Prognosis	7-8
1.7 Differential Diagnosis	8
1.8 Diagnostic Studies	8-13
1.9 Prevention	13
1.10 Treatment	14-15

Chapter Two (Research Methodology) 16
2.0 Methods and Materials
2.1 Study Design and Site 17
2.2 Study Period 17
2.3 Study Population and Patients Selection 17
2.4 Data Collection 17-18
2.5 Inclusion Criteria 18
2.6 Exclusion Criteria 18-19
2.7 Statistical Methods & analysis 19
2.8 Ethical Approval 20

Chapter Three (Results of the Study) 21
3.0 Results 22
3.1 Patients with PSC: Demography & Disease profile 23-24
3.2 Further Results
3.2.1 PSC and influence of Gender and Smoking 25
3.2.2 PSC and influence of Ethnicity 26
3.3 Black African patients with PSC 27
3.4 Black African patients with PSC versus Other race groups with PSC
3.4.1 Demography 28
3.4.2 Clinical findings 28
3.4.3 Blood results 29
3.4.4 Autoimmune profile 30
3.4.5 Imaging findings 31
3.4.6 Bile duct involvement 32
3.4.7 Liver biopsy findings 33
3.5 Black African patients with PSC-IBD versus Other race groups with PSC-IBD
3.5.1 Demography 34
3.5.2 Clinical findings 35
3.5.3 Blood results 36

3.5.4 Autoimmune profile 37
3.5.5 Imaging findings 38
3.5.6 Bile duct involvement 39
3.5.7 Liver biopsy findings 40
3.6 Patients with PSC alone versus Patients with both PSC-IBD
3.6.1 Demography 41
3.6.2 Clinical findings 42
3.6.3 Blood results 43
3.6.4 Autoimmune profile 44
3.6.5 Imaging findings 45
3.6.6 Bile duct involvement 46
3.6.7 Liver biopsy findings 47
3.6.8 Cholangiocarcinoma 47
3.7 Patients with UC alone versus Patients with both UC & PSC 48-49
3.8 Patients with CD alone versus Patients with both CD & PSC 50-53

Chapter Four (Discussion and Conclusion) 54
4.0 Discussion and Conclusion
4.1 Discussion 55-61
4.2 Limitations 62
4.3 Recommendations 62
4.4 Conclusion 63

References 64-70

Appendices

A. Data Collection Sheet 71-72
B. Ethics Clearance Certificate 73
C. Protocol Approval form 74

List of abbreviations

- ANA Anti-Nuclear Antibodies
- ASMA Anti-Smooth Muscle Antibodies
- ALP Alkaline Phosphatase
- ALT Alanine Transaminase
- AST Aspartate Transaminase
- ASCA Anti *Saccharomyces cerevisiae* Antibodies
- CMJAH Charlotte Maxeke Johannesburg Academic Hospital
- CD Crohn's Disease
- CRP C Reactive Protein
- Ca Calcium
- CL Cholesterol
- EHD Extra Hepatic Ducts
- ERCP Endoscopic Retrograde Cholangiopancreatography
- ESR Erythrocyte Sedimentation Rate
- GI Gastro Intestinal Tract
- GGT Gamma Glutamyl Transferase
- HDL High Density Lipoprotein
- HLA Human Leucocyte Antigen
- Hb Hemoglobin
- IBD Inflammatory Bowel Disease
- Ig Immunoglobulin
- INR International Normalized Ratio
- IHD Intra Hepatic Ducts
- LDL Low Density Lipoprotein
- LOW Loss Of Weight
- MRCP Magnetic Resonance Cholangiopancreatography
- Mg Magnesium

- PSC Primary Sclerosing Cholangitis
- P-ANCA Perinuclear Anti Neutrophil Cytoplasmic Antibodies
- Ph Phosphate
- UC Ulcerative Colitis
- US Ultra Sound
- USA United States of America
- TG Triglycerides
- WBC White Blood Count

List of figures

Content		***Page Number***
Figure 1.1	ERCP findings in PSC*	10
Figure 1.2	MRCP findings in PSC*	11
Figure 1.3	US findings in PSC*	11
Figure 1.4	Liver Biopsy findings in PSC*	12
Figure 1.5	Liver Biopsy findings in IgG4 variant*	13
Figure 3.1	Clinical findings in PSC at time of initial presentation	24

* This Figure/Image is copied in terms of Section 12 (Fair Dealing) of the S.A. Copyright Act No. 98 of 1978 (as amended).

List of tables

Content		***Page Number***
Table 3.1	Demography and Disease Profile in PSC patients	23
Table 3.2	PSC and Gender and Smoking influence	25
Table 3.3	PSC and Ethnicity influence	26
Table 3.4	Demography & Disease Profile in Black African PSC Patients	27
Table 3.5	Demography in Black African PSC vs other race group with PSC	28
Table 3.6	Clinical findings in Black African PSC vs other race group with PSC	28
Table 3.7	Blood Results in Black African PSC vs other race group with PSC	29
Table 3.8	Autoimmune Profile in Black African PSC vs other race group with PSC	30
Table 3.9	Imaging Findings in Black African PSC vs other race group with PSC	31
Table 3.10	Bile Duct Involvement in Black African PSC vs other race of PSC	32
Table 3.11	Liver Biopsy Findings in Black African PSC vs other race of PSC	33
Table 3.12	Demography in Black African PSC-IBD vs other race group with PSC-IBD	34
Table 3.13	Clinical findings in Black African PSC-IBD vs other race group with PSC-IBD	35
Table 3.14	Blood Results in Black African PSC-IBD vs other race group with PSC-IBD	36
Table 3.15	Autoimmune Profile in Black African PSC-IBD vs other race group with PSC-IBD	37
Table 3.16	Imaging Findings in Black African PSC-IBD vs other race group with PSC-IBD	38
Table 3.17	Bile Duct Involvement in Black African PSC-IBD vs other race group with PSC-IBD	39
Table 3.18	Liver Biopsy Findings in Black African PSC-IBD vs other race group with PSC-IBD	40
Table 3.19	Demography in PSC versus PSC and IBD	41
Table 3.20	Clinical findings in PSC versus PSC and IBD on initial presentation	42

Table 3.21 Blood Results in PSC versus PSC and IBD 43
Table 3.22 Autoimmune profile in PSC versus PSC and IBD 44
Table 3.23 Imaging findings in PSC versus PSC and IBD 45
Table 3.24 Bile duct involvement in PSC versus PSC and IBD 46
Table 3.25 Liver biopsy findings in PSC versus PSC and IBD 47
Table 3.26 Prevalence of cholangiocarcinoma in PSC versus PSC and IBD 47
Table 3.27 Age comparison between UC alone and UC with PSC 48
Table 3.28 Extra GI manifestations in UC alone and UC with PSC 49
Table 3.29 Colon involvement in UC alone and UC with PSC 49
Table 3.30 Age comparison between CD alone and CD with PSC 50
Table 3.31 Extra GI manifestations in CD alone and CD with PSC 51
Table 3.32 Upper and Lower GI involvement in CD and CD with PSC 52
Table 3.33 Lower GI involvement in CD and CD with PSC 53

CHAPTER ONE

LITERATURE OVERVIEW

1.0 Introduction:

1.1 Definition

Primary Sclerosing Cholangitis (PSC) is a chronic liver disease characterized by a progressive course of cholestasis associated with inflammation and fibrosis of both intra hepatic and extra hepatic bile ducts.[1,2] The term ‘primary’ is used to differentiate PSC from other forms that are secondary to other diseases, such as choledocholithiasis, bacterial cholangitis, prior biliary surgery, and acquired immunodeficiency syndrome associated with cholangiopathy. The term "sclerosing" describes the hardening and scarring of the bile ducts that result from the chronic inflammation and "cholangitis" refers to inflammation of bile ducts. These changes cause the accumulation of bile within the liver. This obstruction to bile flow damages the liver cells; a consequence of the toxicity of the retained bile. This results in inflammation and scarring which could affect the entire liver and the system of bile ducts leading to liver cirrhosis.

1.2 Epidemiology

PSC is an uncommon disease with only a few population-based studies having looked at its incidence and prevalence. The epidemiology of the condition has not been well delineated. A review from 2011 estimated that the general incidence rate was 0.77 per 100 000 person-years; but there were significant differences among the studies. This value may not be a true global reflection as the eight studies included in this review were all from North America and Europe.[3] Each of the eight studies noted an increased incidence during the study period. This rise in incidence was confirmed in the serial studies of PSC in Japan.[4]

The prevalence of PSC varies considerably amongst countries. In a recent review the prevalence ranged from 0.22/ 100 000 (Spain) to 13.6/ 100 000 (United States). Ten studies were included in this review; nine of which were from the United States (US) or Europe. The other study was from Japan where there was an estimated prevalence of

0.95/100 000. This review highlighted the varied prevalence of PSC.[4] The prevalence of PSC is possibly increased in first degree relatives.[5]

Unfortunately, there are no significant studies documenting the prevalence of PSC in Africa. A possible reason for this lack of information is the limited access to advanced health care and the necessity for Endoscopic Retrograde Cholangio-Pancreatography (ERCP) and/or Magnetic resonance cholangiopancreatography (MRCP) to confirm the diagnosis.

The studies to date have all noted that the majority of patients with PSC are male. In the studies from Norway and Sweden 71% of the affected patients were male. This was in contrast to the Japanese study were only 54% were male. The age at diagnosis varies between 37 and 55 years.[4]

The differences in the epidemiological data recorded suggest that the presentation of PSC may vary in different populations.

1.3 Aetiology

The aetiology of this disease remains unknown. It is thought to be multifactorial, and includes the following:

- autoimmune mechanism
- genetic predisposition
- environmental factors

The autoimmune mechanism has been suggested because approximately 75-90% of patients with PSC have concomitant Inflammatory Bowel Disease (IBD). Most of the patients (87%) have ulcerative colitis (UC) and the remainder (13%) have Crohn's Disease (CD). However, only approximately 4% of patients with IBD have or develop PSC.[6,7] A marked increase in serum autoantibody levels occurs in patients with PSC as

well, with perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) in 30-80%, antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) in 10-20% of patients.[8] The study by Muratori et al detected antibodies to the baker's yeast *Saccharomyces cerevisiae* in up to 44% of patients with PSC. This was irrespective of the presence of IBD.[9] The significance of this finding is yet to be determined.

There are very few population-based studies evaluating PSC but there are two important factors which appear to influence the global distribution of the disease i.e. differences in Human Leukocyte Antigen (HLA) susceptibility among ethnic groups and an inconstant frequency of IBD worldwide.[10,11]

The genetic predisposition has been proposed due to the increased prevalence of HLA-B8, HLA-DR2, HLA-DR3 HLA-DR4 and HLA-Drw52a in PSC patients.[6] HLA-B8 has been detected in 60 to 80% of patients with PSC, and only 25% of control subjects. The presence of HLA-DRw52a and -DR4 are likely increase the risk for severe or progressive disease.[12] PSC also tends to cluster in first degree relatives and siblings; further supporting the genetic predisposition, however no specific pattern of inheritance exists.[5, 13]

Regarding the environmental effect, globally there is geographical variation in the prevalence of PSC with similar rates in North American and Northern European countries but lower rates in Asia and Southern Europe.[8,14, 15] The geographical distribution of PSC mirrors that of Ulcerative Colitis (UC), and this may account for the geographical disparity.[11]

Smoking was found to be a protective factor against PSC, independent from the IBD subtype.[6, 16] This finding was recently confirmed by a Norwegian study which also found that coffee exerted a similar protective effect in males.[17] The exact mechanism of the protection is unclear but could be related to the effects of their active ingredients. Of interest is that key substances in cigarettes and coffee (nicotine and caffeine,

respectively) have a comparable effect; both are sympathomimetic and may increase the intra cellular levels of cyclic adenosine monophosphate which mediates by unknown mechanism this kind of protection.[17]

1.4 Disease presentations

A large number of patients present without symptoms, especially in the early stages of the disease and come to attention simply by a finding of persistently abnormal liver tests. These asymptomatic patients have a reduced life expectancy in comparison to the general population since up to 17% can have cirrhosis at diagnosis.[18-19]

Symptoms, when present are vague and nonspecific, and are of little help in confirming the diagnosis. The patients typically experience alternating stages of exacerbation and remission. Fatigue is the most common symptom.[5] The sudden onset of pruritus could signal the possibility of obstruction of the biliary tree. The other symptoms are those associated with advanced liver disease such as jaundice, abdominal distension, confusion and gastrointestinal bleeding. The symptoms encountered in PSC may remit and then recur spontaneously. Some patients may have fever and pain arising from cholangitis and other patients experience chronic right upper quadrant discomfort; however, right upper quadrant pain is not a prominent feature of PSC. Many patients with PSC have IBD; hence, bleeding from the colon should lead to considerations of IBD or portal hypertension. Rarely PSC can present as acute liver failure. This diagnosis should be entertained in patients with IBD who present with acute liver failure of unspecified aetiology.[20]

There are other variant presentations for PSC including:

- Overlap syndrome
- IgG4 associated cholangitis
- Small duct PSC

“Overlap syndrome” is used to describe variant forms of autoimmune hepatitis (AIH) which present with characteristics of AIH and primary sclerosing cholangitis (PSC) or primary biliary cirrhosis (PBC). Patients with PSC-Overlap syndromes present with both hepatitic and cholestatic serum liver pictures and have histological features of AIH and PSC.[21]

Immunoglobulin G4 (IgG4) associated cholangitis” is the hepatobiliary manifestation of a recently characterized inflammatory systemic disease, associated with an increased IgG4 serum level and IgG4-positive lymphoplasmacytic infiltration. It can impersonate PSC. The hallmark features are biliary strictures, lymphoplasmacytic tissue infiltration and raised serum IgG4 levels. These features often occur in conjunction with parenchymal pancreatic findings and pancreatic duct irregularities.[22] Cholangiography cannot consistently differentiate between PSC and IgG4 associated cholangitis.[23] Serum IgG4 levels and pancreatic anatomy on cross-sectional imaging are important tools to assist in differentiating between these two entities. IgG4 can be responsive to steroids and is therefore important to diagnose.[24]

“Small duct PSC” is a variant where the bile ducts are normal on cholangiography (MRCP and ERCP) but have the same cholestatic and histologic picture of PSC.[24]

Jaundice, weight loss, and occasionally pruritic skin marks may be significant clinical findings. Hepatic enlargement occurs commonly; and splenomegaly is present in up to one third of patients. Disease progression can lead to signs of liver cirrhosis.

1.5 Disease complications

Patients with PSC are susceptible to repeated episodes of bacterial cholangitis, with progressive biliary scarring and obstruction. They are also predisposed to develop pigmented biliary stones.

Chronic cholestasis leads to the reduced availability of conjugated bile acids in the small intestine. This results in steatorrhea; a deficiency of the fat-soluble vitamins; metabolic bone disease with osteoporosis and calorie deficit with ensuing weight loss.[25] Secondary biliary cirrhosis can be a consequence of chronic cholestasis in patients with PSC. This results in portal hypertension with variceal bleeding, ascites and liver failure.

The most dreaded complication of PSC is cholangiocarcinoma. The reported lifetime prevalence ranges between 10% and 30%.[6] The risk of developing cholangiocarcinoma cannot be established for any specific patient. There are no reliable serologic tumour markers. Deteriorating jaundice, pruritus or weight loss could signal the development of a stricture or cholangiocarcinoma. Dominant biliary strictures can be recognized in approximately 20% of patients with PSC. They need to be distinguished from cholangiocarcinoma. The strictures can lead to cholestasis with jaundice; pruritus and may end in cholangitis.

Patients with PSC and UC have an increased risk (25%) of developing colorectal malignancy compared to patients with UC alone (5.6%).[6]

1.6 Disease prognosis

PSC is generally a progressive disease that eventually culminates in liver cirrhosis or death. The median survival to death or liver transplantation is approximately 12 years. This result is similar in studies from Sweden,[26] the USA[27] and England.[10] In the largest study by Broome et al, almost two thirds of the patients (66%) were symptomatic at diagnosis and almost one quarter (26%) demised due to cholangiocarcinoma. The median time to diagnosis of cholangiocarcinoma was 32 months after the diagnosis of PSC.[26]

The revised Mayo Clinic model for survival probability in patients with PSC includes the following:

- Age
- Serum bilirubin, albumin, and aspartate aminotransferase levels
- Variceal bleeding history [28]

1.7 Differential Diagnosis of PSC

PSC can be difficult to differentiate from secondary causes of sclerosing cholangitis i.e. stone disease; infection; pancreatitis; surgical/procedural trauma and malignancy.

The histopathological and imaging findings in both PSC and secondary sclerosing cholangitis are similar i.e. the multifocal biliary strictures which eventually cause destruction of bile ducts and secondary biliary cirrhosis.[24] PSC is a diagnosis of exclusion and causes of secondary sclerosing cholangitis need to be excluded.

1.8 Diagnostic studies

The diagnosis of PSC is based on the combination of characteristic imaging findings in conjunction with clinical, biochemical, and histological features. It is essential to rule out secondary causes such as biliary neoplasms; previous biliary surgery; biliary stones; drug-induced bile duct injury and chronic bacterial cholangitis.

<u>Biochemical studies:</u>

PSC patients characteristically present with a cholestatic pattern of liver enzyme abnormalities. The alkaline phosphatase enzyme (ALP) is typically three to five times the upper limit of normal and the gamma-glutamyl transferase (GGT) is raised. The aminotransferase levels are not significantly raised.[8] An elevated level of serum bilirubin (BR) may indicate the presence of advanced disease or herald the onset of

complications such as cholangiocarcinoma, biliary stones and bacterial cholangitis. At the time of diagnosis, the levels of serum albumin are usually normal, and they can become progressively abnormal as the disease advances.

In patients with PSC the serum carbohydrate antigen (CA) 19-9 is often used as a screening test for cholangiocarcinoma. The disadvantage of this investigation is the lack of specificity as the levels can be increased in several disorders both benign and malignant. The conditions associated with an abnormal serum CA 19-9 level include PSC without cancer, alcoholic liver disease, cholangitis, autoimmune hepatitis; chronic viral hepatitis, pancreatitis, cholangiocarcinoma, pancreatic cancer and hepatocellular carcinoma.

Autoimmune screen:

Autoantibodies, hypergammaglobulinemia, and abnormal copper accumulation are also common laboratory findings.[6] The PSC patients show marked increase in serum autoantibody levels with perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) antibodies in 30-80%, Anti-nuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) in 10-20% of patients.[8] Serum immunoglobulin (Ig) levels are typically increased, especially IgG and IgM. The levels of serum IgG4 levels are generally within the normal range; however, they can be increased in around 9% of patients (>140mg/dL).[29] The patients with raised IgG4 have a lower occurrence of associated IBD, higher PSC Mayo risk scores and a reduced interval to liver transplantation. It is possible that they represent a more severe course of disease.[29] The pancreatogram may be abnormal; making it difficult to distinguish the condition from autoimmune sclerosing pancreatitis.[30,31]

Imaging studies:

Previously ERCP was considered the gold standard for the diagnosis of PSC, but recent studies have shown that MRCP is a valuable technique both in the diagnosis and follow up of patients with PSC. It has a similar sensitivity and specificity to ERCP.[6, 28, 32]

Mendes and Lindor have suggested that MRCP may be superior to ERCP for intrahepatic visualization.[6]

The typical cholangiographic findings of PSC include multifocal strictures and dilatations that have a classic beaded appearance and may form diverticular outpouchings. In most cases, these findings affect both intra and extra-hepatic bile ducts, but they can occur in isolation.[6]

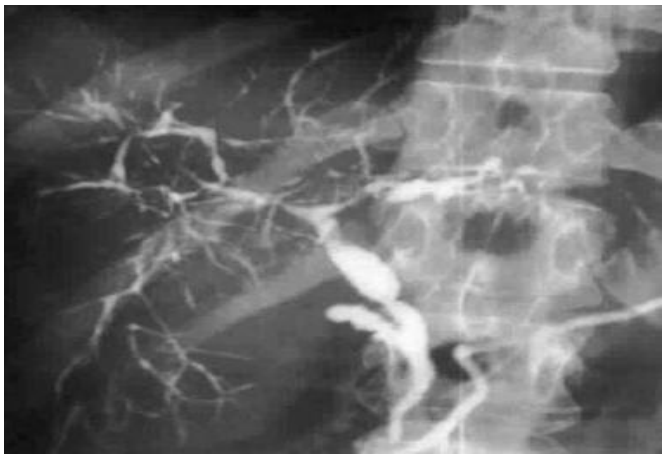


Figure 1.1: ERCP Findings in PSC (beading appearance of bile ducts)[33]

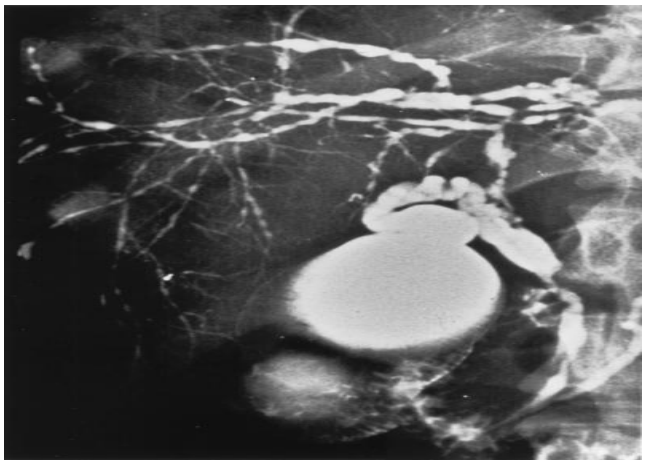


Figure 1.2: MRCP Findings in PSC (beading appearance of bile ducts)[34]

The ultrasound is usually normal in PSC. Experienced radiologists may detect subtle changes e.g. thickening of the gallbladder wall and bile duct; enlarged gallbladder volume or biliary tract dilatation.[35] These changes are not pathognomonic of PSC but are indicative and can often lead to its ultimate diagnosis.

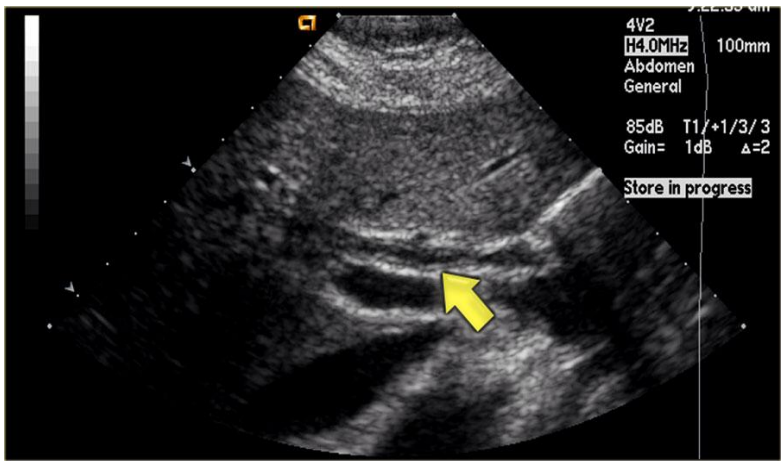


Figure 1.3: Ultrasound Findings in PSC (thickening of bile duct wall)[36]

<u>Histopathological studies:</u>

The liver biopsy in PSC assists more with staging rather than in the establishment of the diagnosis itself. The histologic findings in PSC are usually not specific as the typical onion-skin fibrosis only occurs in a small proportion (10%) of patients.[6]

Ludwig et al described a staging system for PSC.[6] There are four stages:

- Stage I is characterized by portal hepatitis
- Stage II is characterized by fibrosis or hepatitis involving the periportal area
- Stage III is characterized by septal fibrosis or bridging necrosis
- Stage IV is characterized by biliary cirrhosis

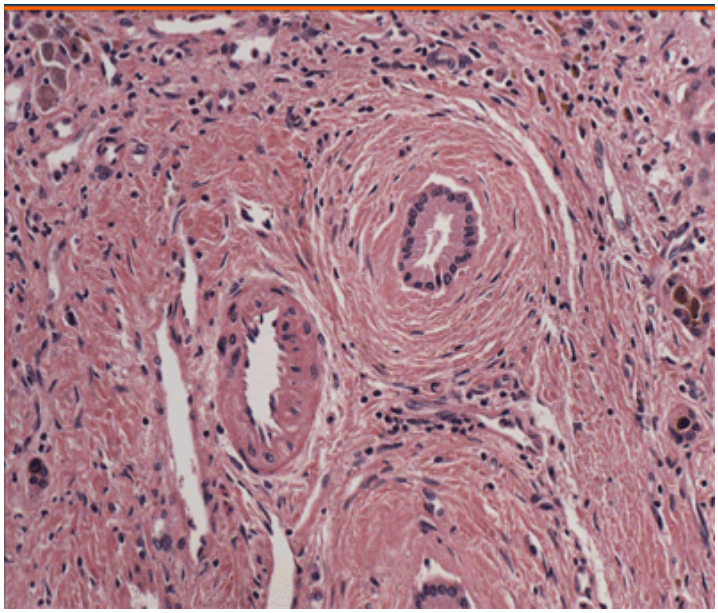
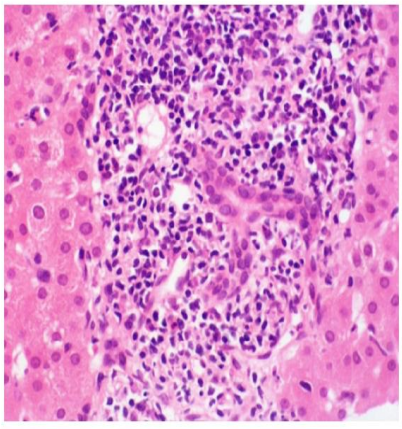


Figure 1.4: Liver Biopsy Findings in PSC[37]



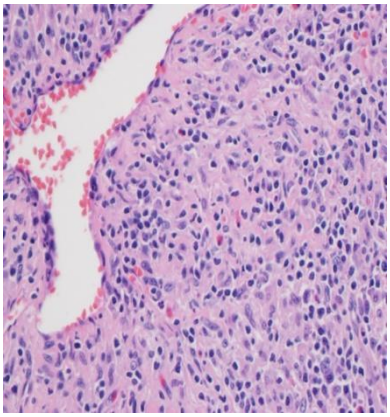


Figure 1.5: Liver Biopsy Findings in IgG4 Variant [38]

(IgG4-positive lymphoplasmacytic infiltration)

1.9 Prevention

Prevention of PSC is not a viable option at this stage as a specific cause has not been identified. Cirrhosis is often presumed to be secondary to the excessive consumption of alcohol. There is no proven association between PSC and alcohol.

The currently accepted theory is that the disease results from the interaction between an unknown bacterial or viral organism in people with an underlying genetic predisposition. The viruses that commonly cause hepatitis have not shown an association with PSC. [6,9]

The common co-existence of PSC and IBD points to either a shared cause for both diseases or that the inflamed colon permits infections and the absorption of toxins. This results in inflammation of the bile duct.[6,9]

1.10 Treatment

The pharmacologic treatment in PSC is not very effective. The drug urosodeoxycholic acid (UDCA) provides symptomatic relief. The use of immunosuppressants; chelators and steroids have not shown significant benefit in halting disease progression.[16] In patients with IgG4 variant cholangiopathy the use of steroids is beneficial.[24]

The following measures are encouraged:

- Dietary medium-chain triglycerides and supplementation of fat soluble vitamins in patients with steatorrhea.
- Pancreatic enzyme deficiency requires oral enzymatic replacement.
- Calcium supplementation in patients with bone disease is recommended
- Physical activity should be encouraged but in patients with osteoporosis, the possibility of fractures should determine the types of activity encouraged.

Endoscopic therapy is achievable only for larger bile ducts. Biliary obstruction however may occur at any level of the biliary tree including the microscopic biliary ductules and the extrahepatic bile ducts. This procedure is earmarked for patients with significant bile duct stenoses limited to the large intra and extrahepatic bile ducts. These are termed dominant strictures. In a select group of patients with dominant strictures endoscopic intervention has the following benefits:

- It relieves the complications of pruritus and cholangitis.
- It allows early detection of cholangiocarcinoma and may lead to an improved survival.[8, 16, 24]

Surgical reconstruction of the biliary tree can result in clinical improvement, specifically jaundice and cholangitis. The procedure is not without risks and can lead to:

- Infection related cholangitis and an associated increased rate of mortality.[39]
- Post-operative scarring which increases the difficulty of liver transplantation.[40]

Liver transplantation is the only therapeutic intervention that improves survival and quality of life in the vast majority of patients (80%).[6] This has led to the discontinuation of surgical drainage procedures.[40]

CHAPTER TWO

RESEARCH METHODOLOGY

2.0 Methods and Materials:

2.1 Study design and site

This is was a retrospective chart review of 305 patients with PSC and or IBD conducted at the Gastroenterology Clinic at CMJAH, a tertiary level teaching hospital, affiliated to the University of Witwatersrand.

2.2 Study period

Patients included in the study were evaluated in the clinic between January 1, 2008 and May 31, 2014.

2.3 Study population and patient selection

Patients diagnosed and treated as either PSC or IBD at the Department of Gastroenterology, CMJAH. Patients with PSC either in isolation or with concomitant IBD were identified and their details analysed.

2.4 Data collection

Hospital medical records were used to access patient demographics and relevant medical history. In this study, subjects with PSC were identified by characteristic histopathology while the IBD subjects were identified by colonoscopy and confirmed with histopathology. The relevant data (as outlined in the data collection sheet) was obtained from either the patients' clinic records or National Health Laboratory Systems (NHLS) records.

Histopathology specimens were staged according to the staging system for PSC described by Ludwig et al. They designated four stages [6]:

- Stage I is characterized by portal hepatitis
- Stage II is characterized by fibrosis or hepatitis involving the periportal area
- Stage III is characterized by septal fibrosis or bridging necrosis

- Stage IV is characterized by biliary cirrhosis

The Endoscopic findings on colonoscopy used to define the IBD disease are [41-43]:

- In patients with UC: continuous erythema with edematous mucosa, loss of vascular markings, mucosal friability, erosions and ulcers with inflammatory pseudo polyps.
- In patients with CD: discontinuous erythema, cobblestone appearance, and/or aphthous ulcerations arranged in a longitudinal fashion.

The Histopathological findings used to confirm the endoscopic diagnosis of IBD are [44-46]:

- In patients with UC: superficial inflammation involving the mucosa and to lesser extent the submucosa, cryptitis, crypt abscesses and distortion or loss of crypt architecture.
- In patients with CD: transmural inflammation involving the entire intestinal wall, non-caseating granulomas with/without long and deep fissure-like ulcers.

2.5 Inclusion criteria

- Patients aged 14 years and older with PSC or IBD, selected and identified using hospital medical records.
- The diagnosis of PSC was based on the presence of characteristic features on radiographic imaging (ERCP or MRCP) or on liver biopsy.
- The diagnosis of IBD was based on the clinical presentation as well as colonoscopyy, radiologic and pathological findings.

2.6 Exclusion criteria

- Patients in whom the diagnostic procedures were done at an outside institution.
- Patients with liver abnormalities that could be attributed to drug induced liver injury.

- Patients who have other aetiologies which could account for the PSC- like features e.g. HIV and secondary cholangitis (cholangitis secondary to infection of bile ducts).

2.7 Statistical Methods and analysis;

Statistical Package

The data was captured in Microsoft Excel and later exported into Statistical Product and Service Solutions (SPSS) software where the analysis was conducted.

Descriptive Statistics

Descriptive statistics such as the frequency distribution, mean and standard deviation were conducted to summarise the data. Bar graphs were used to present a pictorial view of frequencies.

Chi-square test

Chi-square test of association was used to assess whether there was an association between two categorical variables such as gender and the presence of PSC. A Chi-square test p-value less than 0.05 is an indication that there is a significant relationship between the two variables while a p-value of greater than 0.05 is an indication of no association between the variables.

Independent samples t-test

Independent sample t-test was used to compare the mean values for patients that had an uptake against those that did not have an uptake. The samples were independent in the sense that they were drawn from different populations and each element of one sample is not matched with a corresponding element of the other sample (Park, H.M, 2009). A p-value less than 0.05 is an indication that there is a significant difference between the two means while a p-value of greater than 0.05 is an indication of no significant difference between the mean values.

2.8 Ethics approval;

Clearance Certificate Number: M140874.

See Appendix B

CHAPTER THREE

RESULTS OF THE STUDY

3.0 Results:

The study population composed of 305 subjects, including 119 Black African patients.

- The cohort of patients with PSC consisted of 69 patients.
    - There were 35 patients with PSC alone
        - 22 patients were Black African
    - There were 34 patients with PSC-IBD
        - 25 patients were Black African

Outline of The Results is as follows;

3.1 Patients with PSC: Demography and disease profile

3.2 Further Results

3.2.1 PSC and the influence of Gender and Smoking

3.2.2 PSC and the influence of Ethnicity

3.3 Black African Patients with PSC: Demography and disease profile

3.4 Black African Patients with PSC versus other race groups with PSC

3.5 Black African Patients with PSC-IBD versus other race groups with PSC-IBD

3.6 Patients with PSC alone versus Patients with both PSC and IBD

3.7 Patients with UC alone versus Patients with both UC and PSC

3.8 Patients with CD alone versus Patients with both CD and PSC

The identification of all patients included in the study was based on the relevant medical institution records.

3.1 Patients with PSC

The cohort with PSC in the study group (both with and without IBD) was made up of 69 patients. The demography and disease profile of this cohort is represented in the table. 3.1 below.

Table 3.1: The demography and disease profile in patients with PSC

Patient characteristics		**Total number**	**Percentage**
Females		35	51%
Males		34	49%
Black Africans		47	68%
Other Ethnic Groups	White	10	15%
	Asians	9	13%
	Coloured	3	4%
PSC alone		34	49%
PSC + IBD		35	51%
Initial presentation * PSC IBD PSC + IBD		 41 19 9	 59% 26% 13%
Clinical findings** Jaundice		 27	39%
Other associated diseases*** Overlap syndrome Hepatitis C		 8 1	12% 1.4%
Age at diagnosis in females		42 years	
Age at diagnosis in males		39 years	

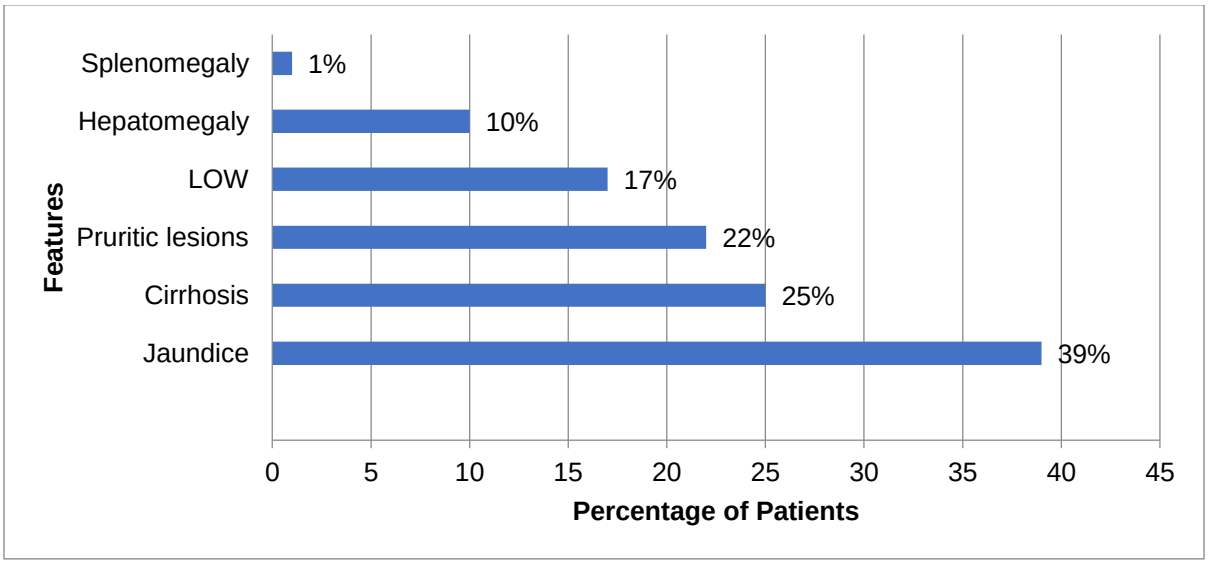


****Figure 3.1: Clinical findings in PSC at time of initial presentation**

As seen in the Figure 3.1, jaundice was the most common clinical finding on initial presentation irrespective of IBD status (39%).

3.2 Further Results

3.2.1 PSC and the influence of gender and smoking

We tested the association between PSC and the following parameters: Gender and Smoking. There was no significant gender difference in the PSC cohort (p = 0.162). On the other hand, there was significant relationship between PSC disease and smoking. We concluded that smoking has a protective effect against PSC (p = 0.015). See Table 3.2 below for details.

Table 3.2: PSC and gender and smoking influence

		Primary sclerosing cholangitis		P value
		Yes	No	
Gender	Male	34 (26.6%)	94 (73.4%)	0.162
	Female	35 (19.8%)	142 (80.2%)	
Smoking	Yes	7 (11.7%)	53 (88.3%)	0.015
	No	62 (25.3%)	183 (74.7%)	

3.2.2 PSC and the influence of ethnicity

We tested the association between PSC and ethnicity. There was no significant ethnicity difference in the PSC cohort" (*p* = 0.297*).* See Table 3.3 below for details.

Table 3.3: PSC and ethnicity

Ethnicity		PSC and IBD		Total
		Both PSC and IBD	PSC only	
African Black	Count	25	22	47
	%	71.4%	64.7%	68.1%
White Caucasian	Count	6	4	10
	%	17.1%	11.8%	14.5%
Asian	Count	2	7	9
	%	5.7%	20.6%	13.0%
Coloured	Count	2	1	3
	%	5.7%	2.9%	4.3%
Total	Count	35	34	69
	%	100.0%	100.0%	100.0%

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.689[a]	3	0.297
N of Valid Cases	69		

a. 5 cells (62.5%) have expected count less than 5. The minimum expected count is 1.48.

3.3 Black African Patients with PSC

The Black African cohort with PSC/ PSC-IBD was made up of 47 patients. The demography and disease profile of this cohort is represented in the table 3.4 below.

Table 3.4: The demography & disease profile in Black African Patients with PSC

Patient characteristics	Total number	Percentage
Females	21	45%
Males	26	55%
PSC	22	47%
PSC + IBD	25	53%
Age at diagnosis in females	40 years	
Age at diagnosis in males	38 years	

3.4 Black African Patients with PSC compared to other race groups of PSC

3.4.1 Demography

There was no statistically significant difference in age at diagnosis, and gender between the two groups. See Table 3.5 below for details.

Table 3.5: Demography in Black African patients with PSC vs other race groups with PSC

		Black African PSC	other race groups with PSC	P-value
Age at diagnosis		43.33 (SD = 19.289)	42.05 (SD = 17.100)	0.842
Gender (%)	Male	33.3	45.5	0.717
	Female	66.7	54.5	0.864

3.4.2 Clinical Findings

There was no statistically significant difference in the clinical findings on the initial presentation. See Table 3.6 below for details.

Table 3.6: Clinical findings in Black African PSC vs other race groups with PSC

Clinical Findings on initial presentation	Black African		other race groups with PSC		P-value
	Number	%	Number	%	
Jaundice	8	36.4	4	33.3	1.000
LOW	1	4.5	2	16.7	0.279
Hepatomegaly	2	9.1	0	0	0.529
Splenomegaly	0	0	0	0	-
Pruritic lesions	3	13.6	4	33.3	0.211
Cirrhosis	7	31.8	4	33.3	1.000

3.4.3 Blood Results

Other than the difference in mean of white blood cell (WBC), haemoglobin level (Hb) in females and platelet count, all other blood results showed no statistical difference. See Table 3.7 below for details.

Table 3.7: Blood Results in Black African PSC vs other race groups with PSC

Blood results	Black African PSC	other race groups with PSC	P-value
WBC ($10^3/mm^3$)	6.43	12.11	**0.010**
Hb (Male) (g/dl)	12.81	13.73	0.188
Hb (Female) (g/dl)	12.20	12.41	**0.006**
Platelets ($10^3/mm$)	279.05	371.50	**0.036**
Total proteins (g/l)	80.59	75.92	0.202
Albumin (g/l)	39.09	39.42	0.902
Total bilirubin (micromol/l)	71.59	95.67	0.504
Direct bilirubin (micromol/l)	54.55	71.17	0.570
ALP (u/l)	506.09	563.25	0.690
GGT (u/l)	585.55	689.92	0.566
ALT (u/l)	177.86	148.58	0.676
AST (u/l)	170.45	98.08	0.278
INR	1.17	1.17	0.978
CRP (mg/l)	24.97	22.75	0.752
ESR (mm/h)	30.68	35.25	0.717
Calcium (mmol/l)	2.35	2.37	0.780
Magnesium (mmol/l)	0.83	0.82	0.808
Phosphate (mmol/l)	1.18	1.27	0.415
Cholesterol (mmol/l)	4.86	6.69	0.091
HDL (mmol/l)	1.15	1.58	0.062
LDL (mmol/l)	3.07	4.54	0.171
Triglyceride (Male) (mmol/l)	1.58	1.84	0.376
Triglyceride (Female) (mmol/l)	1.60	1.50	0.387

3.4.4 Autoimmune Profile

There was no statistically significant difference in the autoimmune profile. See Table 3.8 below for details.

Table 3.8: Autoimmune Profile in Black African PSC vs other race groups with PSC

Autoimmune screen	Black African PSC		other race groups with PSC		P-value
	Number	%	Number	%	
ANA	4	18.2	2	16.7	1.000
P ANCA	2	9.1	0	0	0.529
Anti-SMA	2	9.1	0	0	0.529

3.4.5 Imaging Findings

There was no statistically significant difference in the imaging findings. See Table 3.9 below for details.

Table 3.9: Imaging Findings in Black African patients with PSC vs other race groups with PSC

Type of Imaging	Image findings	Black African PSC		other race groups with PSC		P-value
		Number	%	Number	%	
Ultrasound	Hepatomegaly	2	9.1	0	0	0.529
	Fatty liver	0	0	0	0	-
	Cirrhosis	7	31.8	4	33.3	1.000
	Dilated IHD*	0	0	1	8.3	0.353
	Dilated EHD**	1	4.5	0	0	1.000
	Thick, irreg CBD***	0	0	0	0	-
	Dilated CBD	1	4.5	0	0	1.000
	Splenomegaly	0	0	0	0	-
MRCP and/or ERCP	Beading	11	50	5	41.7	0.729
	Dilatation & Mural irregularities	0	0	0	0	-
	Mural irregularities only	1	4.5	0	0	1.000

Legend: * intra-hepatic duct, ** extra-hepatic duct, ***common bile duct

3.4.6 Bile Duct Involvement

There was no statistically significant difference in the bile duct involvement. See Table 3.10 below for details.

Table 3.10: Bile Duct Involvement in Black African PSC vs other race groups with PSC

Bile duct involved on MRCP & ERCP (%)	other race groups with PSC	Black African PSC	P-value
IHD*, EHD** & CBD***	25	22.7	1.000
IHD, EHD	25	9.1	0.319
IHD, & CBD	0	4.5	1.000
EHD & CBD	0	0	-
IHD only	8.3	31.8	0.210
EHD only	8.3	0	0.353
CBD only	25	22.7	1.000
None	8.3	9.1	1.000

Legend: * intra-hepatic duct, ** extra-hepatic duct, ***common bile duct

3.4.7 Liver Biopsy Findings

There was no significant difference between the liver biopsy findings. See Table 3.11 below for details.

Table 3.11: Liver Biopsy Findings in Black African PSC vs other race groups with PSC

Stages	Black African PSC		other race groups with PSC		P-value
	Number	%	Number	%	
Stage 1	5	22.2	2	20	0.098
Stage 2	2	11.1	8	60	0.342
Stage 3	5	22.2	0	0	0.632
Stage 4	10	44.4	0	0	0.89
Stage 1 with features of drug induced hepatitis	0	0	2	20	1.000

3.5 Black African Patients with PSC-IBD versus other race groups with PSC-IBD

3.5.1 Demography

There was no statistically significant difference in age at diagnosis, and gender distribution. See Table 3.12 below for details.

Table 3.12: Demography in Black African PSC-IBD vs other race groups with PSC-IBD

		Black African PSC-IBD	other race groups with PSC-IBD	P-value
Age at diagnosis		36.8 (SD = 17.100)	45.4 (SD = 19.289)	0.265
Gender	Male	64	40	0.266
	Female	36	60	0.33

3.5.2 Clinical Findings

Cirrhosis was more commonly found in race groups with PSC-IBD compared to the Black African group during their initial presentation. See Table 3.13 below for details.

Table 3.13: Clinical findings in Black African PSC-IBD vs other race groups with PSC-IBD

Clinical Findings on initial presentation	Black African PSC-IBD		other race groups with PSC-IBD		P-value
	Number	%	Number	%	
Jaundice	8	32	7	70	0.062
LOW	7	28	2	20	1.000
Hepatomegaly	4	16	1	10	1.000
Splenomegaly	0	0	1	10	0.286
Pruritic lesions	4	16	4	40	0.186
Cirrhosis	2	8	4	40	**0.043**

3.5.3 Blood Results

The mean platelet count in Black African PSC-IBD group is more than in the other race groups. See Table 3.14 below for details.

Table 3.14: Blood Results in Black African PSC-IBD vs other race groups with PSC-IBD

Blood results	Black African PSC-IBD	other race group with PSC-IBD	P-value
WBC ($10^3/mm^3$)	8.76	10.56	0.458
Hb (Male) (g/dl)	12.17	13.91	0.356
Hb (Female) (g/dl)	12.8	13.76	0.125
Platelets ($10^3/mm$)	351.4	244.8	**0.041**
Total proteins (g/l)	80.36	73.9	0.086
Albumin (g/l)	38.08	38	0.976
Total bilirubin (micromol/l)	83.84	49.4	0.421
Direct bilirubin (micromol/l)	57.6	37.6	0.513
ALP (u/l)	434.44	293.6	0.106
GGT (u/l)	482.12	294.2	0.164
ALT (u/l)	85.56	104.2	0.626
AST (u/l)	82.04	119.6	0.448
INR	1.31	1.18	0.627
CRP (mg/l)	25.1	64	0.171
ESR (mm/h)	35.12	40.4	0.669
Calcium (mmol/l)	2.32	2.27	0.293
Magnesium (mmol/l)	0.85	0.79	0.096
Phosphate (mmol/l)	1.18	1.03	0.133
Cholesterol (mmol/l)	4.35	4.04	0.810
HDL (mmol/l)	1.4	1.49	0.659
LDL (mmol/l)	2.94	2.16	0.535
Triglyceride (Male) (mmol/l)	1.58	1.84	0.169
Triglyceride (Female) (mmol/l)	1.75	1.48	0.564

3.5.4 Autoimmune Profile

There was no statistically significant difference in the autoimmune profile. See Table 3.15 below for details.

Table 3.15: Autoimmune Profile in Black African PSC-IBD vs other race groups with PSC-IBD

Autoimmune screen	Black African PSC-IBD		other race groups with PSC-IBD		P-value
	Number	%	Number	%	
ANA	0	0	2	20	0.076
P ANCA	8	32	0	0	0.073
Anti-SMA	0	0	2	20	0.076

3.5.5 Imaging Findings

Cirrhosis was more commonly found on ultrasound in other race groups with PSC-IBD compared to the Black African group. See Table 3.16 below for details.

Table 3.16: Imaging Findings in Black African PSC-IBD vs other race groups with PSC-IBD

Type of Imaging	Image findings	Black African PSC-IBD		other race groups with PSC-IBD		P-value
		Number	%	Number	%	
Ultrasound	Hepatomegaly	4	16	1	10	1.000
	Fatty liver	0	0	0	0	-
	Cirrhosis	2	8	4	40	**0.043**
	Dilated IHD*	0	0	0	0	-
	Dilated EHD**	0	0	0	0	-
	Thick, irreg CBD***	1	4	0	0	1.000
	Dilated CBD	0	0	1	10	0.286
	Splenomegaly	0	0	1	10	0.286
MRCP and/or ERCP	Beading	14	55.6	5	50	1.000
	Dilatation & Mural irregularities	0	0	1	10	0.286
	Mural irregularities only	3	12	0	0	0.542

Legend: * intra-hepatic duct, ** extra-hepatic duct, ***common bile duct

3.5.6 Bile Duct Involvement

There was no statistically significant difference in the bile duct involvement. See Table 3.17 below for details.

Table 3.17: Bile Duct Involvement in Black African PSC-IBD vs other race groups with PSC-IBD

Bile duct involved on MRCP & ERCP	Black African PSC-IBD		other race groups with PSC-IBD		P-value
	Number	%	Number	%	
IHD*, EHD** & CBD***	7	28	4	40	0.689
IHD, EHD	1	4	1	10	0.496
IHD, & CBD	0	0	0	0	-
EHD & CBD	1	4	0	0	1.000
IHD only	9	36	4	40	1.000
EHD only	0	0	1	10	0.286
CBD only	2	8	0	0	1.000
None	5	20	0	0	0.292

Legend: * intra-hepatic duct, ** extra-hepatic duct, ***common bile duct

3.5.7 Liver Biopsy Findings

There was no significant difference between the liver biopsy findings. See Table 3.18 below for details.

Table 3.18: Liver Biopsy Findings in Black African PSC-IBD vs other race groups

Stages	Black African PSC-IBD		other race groups with PSC-IBD		P-value
	Number	%	Number	%	
Stage 1	7	27.3	6	60	0.439
Stage 2	11	45.5	2	20	0.983
Stage 3	7	27.3	2	20	0.179
Stage 4	0	0	0	0	-
Stage 1 with features of drug induced hepatitis	0	0	0	0	-

3.6 Patients with PSC alone versus patients with both PSC and IBD

3.6.1 Demography

There was no statistically significant difference in age at presentation, ethnicity and gender between patients with PSC alone and those with PSC-IBD. See Table 3.19 below for details.

Table 3.19: Demography in PSC vs PSC-IBD

		PSC-IBD		PSC		P-value
Age at diagnosis		39.26 (SD = 14.593)		42.50 (SD = 17.621)		0.407
		Number	%	Number	%	0.312
Ethnic Group	Black African	25	71.4	22	64.7	
	White	6	17.1	4	11.8	0.256
	Asian	2	5.7	7	20.6	0.189
	Coloured	2	5.7	1	2.9	0.163
Gender	Male	20	57.1	14	41.2	0.22
	Female	15	42.9	20	58.8	0.232

3.6.2 Clinical Findings

There was no statistically significant difference in the clinical findings on the initial presentation. See Table 3.20 below for details.

Table 3.20: Clinical findings in PSC vs PSC-IBD on initial presentation

Clinical Findings on initial presentation	PSC-IBD		PSC		P-value
	Number	%	Number	%	
Jaundice	15	42.9	12	35.3	0.624
LOW	9	25.7	3	8.8	0.110
Hepatomegaly	5	14.3	2	5.9	0.428
Splenomegaly	1	2.9	0	0	1.000
Pruritic lesions	8	22.9	7	20.6	1.000
Cirrhosis	6	17.1	11	32.4	0.171

3.6.3 Blood Results

Other than ALT levels, all other blood results had no statistical difference. See Table 3.21 below for details.

Table 3.21: Blood Results in PSC vs PSC-IBD

Blood results	PSC-IBD	PSC	P-value
WBC ($10^3/mm^3$)	9.3	8.5	0.502
Hb (Male) (g/dl)	12.7	13.0	0.769
Hb (Female) (g/dl)	12.6	13.2	0.423
Platelets ($10^3/mm$)	320.9	311.7	0.773
Total proteins (g/l)	78.5	78.9	0.861
Albumin (g/l)	38.1	39.2	0.502
Total bilirubin (micromol/l)	74.0	80.1	0.812
Direct bilirubin (micromol/l)	51.9	60.4	0.660
ALP (u/l)	394.2	526.3	0.095
GGT (u/l)	428.4	622.4	0.066
ALT (u/l)	90.9	167.5	**0.043**
AST (u/l)	92.8	144.9	0.133
INR	1.3	1.2	0.434
CRP (mg/l)	36.2	24.2	0.215
ESR (mm/h)	36.6	32.3	0.591
Calcium (mmol/l)	2.3	2.4	0.214
Magnesium (mmol/l)	0.8	0.8	0.988
Phosphate (mmol/l)	1.1	1.2	0.306
Cholesterol (mmol/l)	4.3	5.5	0.114
HDL (mmol/l)	1.4	1.3	0.388
LDL (mmol/l)	2.7	3.6	0.257
Triglyceride (Male) (mmol/l)	1.8	1.8	0.946
Triglyceride (Female) (mmol/l)	1.5	1.6	0.651

3.6.4 Autoimmune Profile

There was no statistically significant difference in the autoimmune profile. See Table 3.22 below for details.

Table 3.22: Autoimmune Profile in PSC versus PSC-IBD

Autoimmune screen	PSC- IBD		PSC		P-value
	Number	%	Number	%	
ANA	2	5.7	6	17.6	0.151
P ANCA	8	22.9	2	5.9	0.084
Anti-SMA	2	5.7	2	5.9	1.000

3.6.5 Imaging Findings

There was no statistically significant difference in the imaging findings. See Table 3.23 below for details.

Table 3.23: Imaging Findings in PSC vs PSC- IBD

Type of Imaging	Image findings	PSC-IBD		PSC		P-value
		Number	%	Number	%	
Ultrasound	Hepatomegaly	4	11.4	6	17.6	0.513
	Fatty liver	0	0	3	8.8	0.114
	Cirrhosis	2	5.7	6	17.6	0.151
	Dilated IHD*	0	0	1	2.9	0.493
	Dilated EHD**	0	0	1	2.9	0.493
	Thick, irreg CBD***	1	2.9	0	0	1.000
	Dilated CBD	1	2.9	1	2.9	1.000
	Splenomegaly	7	20	4	11.8	0.513
MRCP and/or ERCP	Beading	21	60	24	70.6	0.801
	Dilatation & Mural irregularities	1	2.9	0	0	1.000
	Mural irregularities only	3	8.6	2	5.9	1.000

Legend: * intra-hepatic duct, ** extra-hepatic duct, ***common bile duct

3.6.6 Bile Duct Involvement

CBD involvement was more common in the PSC group compared to the PSC-IBD group and this was statistically significant (p-value =0.045). See Table 3.24 below for details.

Table 3.24: Bile Duct Involvement in PSC vs PSC-IBD

Bile duct involvement on MRCP & ERCP	PSC-IBD		PSC		P-value
	Number	%	Number	%	
IHD*, EHD** & CBD***	11	31.4	8	23.5	0.592
IHD, EHD	2	5.7	5	14.7	0.259
IHD, & CBD	0	0	1	2.9	0.493
EHD & CBD	1	2.9	0	0	1.000
IHD only	13	37.1	8	23.5	0.297
EHD only	1	2.9	1	2.9	1.000
CBD only	2	5.7	8	23.5	**0.045**
None	5	14.3	3	8.8	0.710

Legend: * intra-hepatic duct, ** extra-hepatic duct, ***common bile duct

3.6.7 Liver Biopsy Findings

There was no significant difference between the liver biopsy findings. See Table 3.25 below for details.

Table 3.25: Liver Biopsy Findings in PSC vs PSC-IBD

Stages	PSC-IBD		PSC		P-value
	Number	%	Number	%	
Stage 1	6	37.5	3	21.4	0.440
Stage 2	6	37.5	4	28.6	0.709
Stage 3	4	25	2	14.3	0.657
Stage 4	0	0	4	28.6	0.037
Stage 1 with features of drug induced hepatitis	0	0	1	7.1	0.467

3.6.8 Cholangiocarcinoma

There were two patients with cholangiocarcinoma in PSC-IBD group versus none in the group with PSC alone. See Table 3.26 below for details.

Table 3.26: Prevalence of Cholangiocarcinoma in PSC vs PSC-IBD

Cholangiocarcinoma	PSC-IBD		PSC		P-value
	Number	%	Number	%	
No	33	94.3	34	100	0.493
Yes	2	5.7	0	0	

3.7 Patients with UC alone versus patients with both UC and PSC (UC-PSC);

A comparison of UC patients with and without PSC was made and shown in the Table 3.27 below.

Conjunctivitis was the only extra-GI manifestation that was statistically significant between the two groups (p-value 0.005). It was not detected in patients with UC. See Table 3.28 below for details.

Pancolitis (on colonoscopy) was significantly more common in PSC-UC patients (56.7%) compared to the UC group (43.3%) with p-value 0.004. See Table 3.29 below for details.

Colon malignancy was reported more commonly in the UC group (four patients) than the PSC-UC group (one patient). Two patients with PSC-UC developed cholangiocarcinoma compared to none in UC during the follow up period of 2-3 years.

Five patients in PSC-UC group required Liver transplantation. None of them showed recurrence of their disease.

Eight PSC-UC patients demised three of them as a result of liver failure, two of them secondary to cholangiocarcinoma and the causes of death were unknown for the remaining three patients. The other PSC patients were reported to be in remission.

Table 3.27: Age comparison between UC alone and UC-PSC

	UC-PSC	UC	P value
Age at study entry	44.40	52.5	0.012
Age at diagnosis	32.6	38.9	**0.040**

Table 3.28: Extra GI manifestations in UC alone and UC-PSC

Extra GI manifestations	UC-PSC		UC		P value
	Number	%	Number	%	
Uveitis	0	0	2	1.4	1.000
Conjunctivitis	3	10	0	0	**0.005**
Erythema nodosum	0	0	4	2.8	1.000
Pyoderma gangrenosum	2	6.7	2	1.4	0.142
Gall stones	1	3.3	2	1.4	0.441
Venous thrombo-embolism	1	3.3	6	4.3	1.000
Arthralgia	4	13.3	24	17	0.788
Arthritis	1	3.3	13	9.2	0.468
Oral ulcers	1	3.3	1	0.7	0.321

Table 3.29: Colon Involvement in UC alone and UC-PSC

	UC-PSC		UC		P value
	Number	%	Number	%	
Proctitis	0	0	9	6.4	1.00

Left colitis	4	13.3	42	29.8	0.095
Right colitis	2	6.7	10	7	1.00
Pan-colitis	17	56.7	61	43.3	**0.004**

3.8 Patients with CD alone versus patients with both CD and PSC (CD-PSC)

There was no significant difference in the age at diagnosis between patients with CD and those with PSC-CD. See Table 3.30 below for details.

None of the Extra GI manifestations was significantly different. See Table 3.31 below for details.

Comparison between the prevalence of upper GI involvement and colonic involvement did not reveal any statistical significance. The PSC itself did not increase the prevalence of colon involvement in those patients with CD. See Tables 3.32 and 3.33 below for details.

One case of colon malignancy was reported with CD group compared to none in the PSC-CD group.

None of the PSC-CD patients developed cholangiocarcinoma or died from liver failure. They were reported to be in remission. Only one patient required a liver transplant and showed recurrence of his disease.

Table 3.30: Age comparison between CD and CD-PSC

	CD-PSC	CD	P-value
Age at Study Entry	47.8	50.5	0.741
Age at diagnosis	43.8	35.3	0.372

Table 3.31: Extra GI manifestations in CD and CD-PSC

Extra GI manifestations	CD-PSC		CD		P-value
	Number	%	Number	%	
Uveitis	0	0	3	3.6	1.000
Conjunctivitis	0	0	1	1.2	1.000
Erythema nodosum	1	25	4	4.8	0.214
Pyoderma gangrenosum	0	0	2	2.4	1.000
Gall stones	1	25	1	1.2	0.090
Venous thromboembolism	0	0	5	6	1.000
Arthralgia	0	0	12	14.5	1.000
Arthritis	0	0	8	9.6	1.000
Oral ulcers	0	0	3	3.6	1.000
Renal stones	0	0	3	3.6	1.000

Table 3.32: Upper and lower GI Involvement in CD and CD-PSC

	CD-PSC		CD		P-value
	Number	%	Number	%	
Normal	0	0	3	3.6	1.000
Proctitis	0	0	2	2.4	1.000
Proctosigmoiditis	0	0	1	1.2	1.000
Left colitis	2	50	10	12	0.090
Right colitis	0	0	12	14.5	1.000
Pancolitis	0	0	4	4.8	1.000
Ileitis	1	25	17	20.5	1.000
Ileocolitis	1	25	32	38.6	1.000
Sigmoiditis	0	0	2	2.4	1.000
Upper GI	0	0	6	7.2	1.000

Table 3.33: Lower GI Involvement in CD and CD-PSC

			CD-PSC	CD	
Lower GI	Small intestine	Count	2	49	51
		%	50	59	58.6
	Large intestine	Count	2	34	36
		%	50	41	41.4
Total		Count	4	83	87
		%	100	100	100

Chi-Square Tests					
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	0.128*	1	0.720		
Continuity Correction**	0	1	1.000		
Likelihood Ratio	0.127	1	0.722		
Fisher's Exact Test				1.000	0.551
Linear-by-Linear Association	0.127	1	0.722		
N of Valid Cases	87				
*2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.66.					
**Computed only for a 2x2 table					

CHAPTER FOUR

DISCUSSION AND CONCLUSION

DISCUSSION

The Primary Sclerosing Cholangitis group;

The incidence of PSC is variable amongst different countries.[11] Ethnicity and varying levels of IBD may account for some of this variability.[47] The incidence of PSC has been reported as 0.9 to1.3 per 100,000 in Northern Europe and the United States of America. In Southern Europe and Asia much, lower levels have been documented (less than 0.1 per 100,000). The frequency of PSC in Africa has not been determined due to the limited availability of diagnostic resources and minimal studies documenting PSC.[48-50]

The real prevalence of PSC is probably higher than the current estimates as cholangiography which is necessary for diagnosis is not widely available.[48] The increase in incidence of PSC in the rest of the world has been extensively documented.[11,49,50]

The occurrence of PSC with concomitant IBD disease has been reported in different studies. The results have been variable. A study by Kozcka et al done in New York in 2014 reviewed 209 patients; self-identified as black. Their retrospective analysis reported the prevalence of PSC (3.1%) among Black African patients with UC. The reported prevalence was lower in their white counterparts (1.3%).[51] The study shows a high prevalence of PSC in black African patients with IBD (71.4%). This was markedly higher than in other race groups where only (28.6%) of patients were affected. Kelly et al previously proposed that Africans with UC have an augmented risk of developing PSC disease.[52,53]

PSC has to date mainly been described in whites.[24,44] There have been very few studies looking specifically at PSC in multi-ethnic populations.
In this cohort, there was no correlation between the ethnicity and PSC disease (regardless of concomitant IBD).
There have been few studies which have described PSC in black populations. Kozcka et al found concomitant PSC in 7 of their 209 black patients (3.5%).[51] Buchel et al have previously commented on the rarity of PSC in black patients. They described 2 black African women with the combination of PSC and CD.[54] In the black African patients in this study, PSC was present in almost one quarter of patients with IBD (25/97), but we only had one black African woman with PSC and IBD. It is difficult to explain the precise reason for the high proportion of PSC in this study. The potential causes include: local environmental factors and underlying genetic susceptibility. The association between PSC and HLA-B8 and -DR3 has been established.[54] Buchel et al proposed that the presence of HLA-B27 in black African patients may pose a risk for the development of PSC and IBD, specifically UC in women.[54]

The PSC diagnosis is generally established before the age of 40 years in males and a little bit later in females.[22,23] The reported median age at diagnosis of PSC is 41 years with the disease occurring earlier in females.[47] The results of this study are consistent with this. The median age of presentation and diagnosis in our patients with PSC (males and females) regardless of the ethnicity and whether IBD disease is present or not was 39 years and 42 years, respectively. In the black African patients in this study a difference in presentation between males (38 years) and females (40 years) was documented.

In this study, the patients with PSC only were slightly older (42.5 years) compared to those with PSC and concomitant IBD (39 years). This difference was not statistically significant. The documented influence of comorbid IBD on the age of diagnosis of PSC has not been consistent.[25,53]

Females (50.7%) and males (49.3%) were almost equally represented in this study. This is contrary to the published literature. The documented ratio of females to males

with PSC disease is variable and ranges between 1:2 and 1:3 in the literature.[6,23,24,48,49] The relatively higher percentage of affected females with PSC in this cohort could be explained by the higher proportion of females (58%) in the study sample. Although the number of black African patients with PSC in this study was small (47), we found a gender bias with males (55.4%) more commonly affected than females (44.6%). This difference between males and females has previously been documented.[6,23,24]

Kozcka et al showed a significant gender bias in their sub-group with PSC and IBD with the majority of their patients (80%) being males.[51] We also found a predominance of males (64%).

The study confirms earlier findings that smoking has a protective effect against PSC.[8,13,17] In 2011 a Norwegian group studied the influence of smoking on PSC patients at Oslo University Hospital. They invited 336 patients to complete their study questionnaire. They concluded that cigarette smoking had a protective effect in patients with PSC irrespective of the presence of concomitant IBD. Interestingly, daily smoking was associated with a higher age at diagnosis of PSC, suggesting it may protect against PSC also by delaying the disease process.[17,55]

The most common clinical finding on initial presentation in symptomatic patients with PSC in our study cohort was jaundice (39%). The black African population in the study also had jaundice as the most common finding on clinical examination (34%). Jaundice on initial presentation has been reported in 10-70% of cases [3,8,18] The underlying IBD status in the study cohorts did not affect the prevalence of jaundice among patients with PSC. Jaundice was reported in 35.3% of patients with PSC alone compared to 42.9% in those with concomitant IBD.

Intra and extra hepatic bile duct involvement was present in most of patients in the study. These findings were documented on imaging studies (MRCP and ERCP) and are consistent with previous descriptions of the disease.[8,22,23] We found beading of the bile ducts in the vast majority of our patients. This is a well described phenomenon on imaging.[8,22,23,56] Isolated CBD involvement was more frequently seen in the PSC group

compared to the PSC-IBD group (23.5% and 5.7% respectively, p-value =0.045). Similar findings have been documented previously.[57] Rabinowitz et al compared clinical; laboratory and radiological findings in patients with isolated PSC to patients with PSC-IBD. In their study involvement of the extrahepatic bile ducts alone was significantly more frequent in patients without inflammatory bowel disease.[58]

The serum ALP enzyme in this study was higher in patients with PSC (5 times the upper limit of normal), irrespective of the ethnicity and underlying IBD status. This finding is supported by other studies on PSC. An increased ALP enzyme is a hallmark feature of PSC and is usually within 3-5 times the upper limit of normal.[8] In this study, the underlying IBD status of our PSC patients had no impact on the raised levels of ALP enzyme.

The pANCA serum antibodies had been reported to be raised in patients with PSC in 30-80% of the cases.[8] We detected pANCA in approximately 15% of patients with PSC. The underlying IBD status had no impact on the levels of pANCA antibodies.

There was no statistical difference in the rest of the blood results, ultrasound, MRCP and ERCP findings between the different ethnic populations of PSC. The results were equivalent for patients with PSC alone compared to those with both PSC and IBD.

Long-term PSC outcomes may/may not be affected by the presence or severity of IBD.[26] In a natural history study of 305 Swedish PSC patients, associated IBD had no significance on the need for liver transplants.[26] A retrospective Israeli study of 141 PSC patients had similar findings. In their patients transplant-free survival rates, cirrhosis rates, and mortality of PSC patients were found to be independent of concomitant IBD.[58] The findings were different in a population-based epidemiologic study of PSC patients from New Zealand, PSC-IBD patients when compared to PSC patients were more likely to require liver transplantation (p=0.03).[59] This study suggests that IBD has an effect on the PSC outcome and increases the rate of liver transplantation. There were too few patients to determine whether this finding is statistically significant. Six patients with

PSC and IBD required a liver transplantation compared to three patients with PSC alone.

Two of the patients with PSC (3%) enrolled in the study developed cholangiocarcinoma during the follow-up. About 10-30% of the patients with PSC develop this neoplasm during the course of their disease.[8] The relatively low figure in this study is possibly a reflection of the short follow up period.

The ulcerative colitis group;

The diagnosis of IBD was earlier in the PSC group (32.6 years) than non PSC group (38.9 years). This figure was unaffected by the ethnicity. The study findings are consistent with the study done by Kozcka et al. In their UC subgroup the age of diagnosis of IBD was 31years in the PSC group compared with 38.7 years in the non-PSC group.[51]

This study reflects the reported literature regarding the prevalence of PSC among patients with IBD. PSC is more common in patients with UC than CD, this is irrespective of ethnicity. There were 30/69 (43.5%) cases with UC and only 4/69 (5.8%) cases in patients with CD. In our black African cohort, the prevalence of PSC among IBD patients was 22/25 (88%) for UC and only 2/25 (8%) for patients with CD. A 25-year study, in Barbados looked at the prevalence of PSC in black patients with IBD. They too found PSC to be more common in patients with UC (10%). They did not detect PSC in any of their patients with CD.[60]

Study data showed that the extent of colon involvement was more prominent in the PSC-UC patients than UC patients. The patients with PSC-UC had a more quiescent course. These findings are compatible with the literature.[61] The data suggests that PSC severity may have a “protective” effect on the activity of the UC. PSC patients, although more likely to have pancolitis; seem to have a more benign course of UC disease activity and the risk of progression to colectomy is not increased.[26,51,61]

This study revealed that colon malignancy was more common in patients with UC alone than in the PSC-UC group (4 patients vs one patient). This finding conflicts with that of Zheng et al. Their meta-analysis of 13,379 patients showed that PSC in patients with UC was accompanied by a threefold increased risk of colorectal malignancy.[62] The

small number of patients makes it difficult to make definitive conclusions, but our results indicate that PSC is less likely to lead to colon malignancy. This finding needs to be explored further.

The Crohn's disease group;

Patients in the study with CD alone presented had an earlier age of diagnosis (35.3 years) in comparison to the group with CD-PSC (43.7 years). These findings are unexpected. In the study by Kozcka et al patients with CD alone were older (36 years) than those with CD-PSC (19.5 years).[51]

None of the CD-PSC patients in this study developed colon cancer, cholangiocarcinoma or died from liver failure. Only one patient required a liver transplant and showed recurrence of his disease. The rest of the patients were reported to be in remission. Kozcka et al reported similar findings. In their study, none of the CD-PSC patients developed cholangiocarcinoma or died from liver failure. Their patients were reported to be in remission.[51] Their mean follow-up time was 37 months following the diagnosis of PSC.

Limitations:

The data in this study was collected retrospectively, therefore its value is limited by completeness and accuracy of clinical information included in the patient's medical records. However, this was not the only limitation to our study. Since it was a single-centre database, the number of patients limits certain analyses and makes it difficult to draw definitive conclusions.

This study was carried out in the public sector and excludes patients who may have sought private care.

Recommendations:

At initial presentation of disease, laboratory testing must be focused at ruling out secondary causes of sclerosing cholangitis.

A full colonoscopy with biopsies is recommended in PSC patients at the time of diagnosis regardless of the symptoms in order to assess for associated colitis.

MRCP and ERCP are useful tools in the diagnosis of PSC and earlier diagnosis of PSC may lead to earlier identification of its complications, including cholangiocarcinoma.

Liver biopsies should be kept for cases in which imaging studies are inconclusive or when the diagnosis of small-duct PSC or an overlap syndrome is being considered.

Conclusion:

Patients in this study with PSC-IBD have a similar profile in terms of demography, clinical, laboratory and imaging findings to previously described large cohorts in the western world.[1]

A notable finding in this study was the high number of black African patients with PSC (with/without IBD), but it lacked statistical significance. This study didn't reveal any association between the PSC (with/without IBD) and ethnicity.

The data in this study supports the observations of other studies that colonic inflammation is important for PSC development particularly with ulcerative colitis. An underlying history of IBD and autoimmune disorders should be sought in patients with PSC.

References:

1. Rossi RE, Conte D, Massironi S. Primary sclerosing cholangitis associated with inflammatory bowel disease: an update. Eur J Gastroenterol Hepatol 2016; 28:123-31.
2. Maggs JR, Chapman RW. An update on primary sclerosing cholangitis. Curr Opin Gastroenterol 2008; 24:377-83.
3. Molodecky N, Kareemi H, Parab R, Herman B, Hude Q, Robert P, Gilaad K. Incidence of primary sclerosing cholangitis: A systematic review and meta-analysis. Hepatology J 2011; 53:1590-99.
4. Tanaka A, Takikawa H. Geoepidemiology of primary sclerosing cholangitis: a critical review. Autoimmun J 2013; 46:35-40.
5. Bergquist A, Lindberg G, Saarinen S, Broome U. Increased prevalence of Primary sclerosing cholangitis among first-degree relatives. J Hepatol 2005; 42:252-56.
6. Mendes F, Lindor K. Primary sclerosing cholangitis. Clin Liver Dis 2004; 8:195-211.
7. Schrumpf E, Elgjo K, Fausa O. Sclerosing cholangitis in ulcerative colitis.Scand J Gastroenterol 1980; 15:689-97.
8. Mee lee Y, Kaplan M. Management of Primary sclerosing cholangitis. Am J Gastroenterol 2002; 97:528-34
9. Muratori P, Muratori L, Guidi M, Maccariello S, Pappas G, Ferrari R, Gionchetti P, Campieri M, Bianchi F. Anti-Saccharomyces cerevisiae antibodies (ASCA) and autoimmune liver diseases. Clin Exp Immunol 2003; 132:473-76.
10. Farrant JM, Hayllar KM, Wilkinson ML, Karani J, Portmann BC, Westaby D, Williams R. Natural history and prognostic variables in primary sclerosing

cholangitis. Gastroenterology 1991; 100:1710-17.

11. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary Sclerosing cholangitis and primary biliary cirrhosis: a Systematic review. J Hepatol 2012; 56(5):1181-88.

12. Van Milligen de Wit AW, Van Deventer SJ, Tytgat GN. Immunogenetic aspects of primary sclerosing cholangitis: implications for therapeutic strategies. Am J Gastroenterol 1995; 90(6):893.

13. Quigley EMM, LaRusso NF, Ludwig J, MacSween RN, Birnie GG, Watkinson G. Familial occurrence of Primary Sclerosing Cholangitis and Ulcerative Colitis. Gastroenterology 1983; 85:1160-65.

14. Escorsell A, Pares A, Rodes J, Solis-Herruzo JA, Miras M, de la Morena E. Epidemiology of primary sclerosing cholangitis in Spain. J Hepatol 1994; 21:787-91.

15. Ang TL, Fock KM, Ng TM, Teo EK, Chua TS, Tan JY. Clinical Profile of Primary Sclerosing Cholangitis in Singapore. J Gastroenterol Hepatol 2002; 17:908-13.

16. Beuers U, Boberg KM, Chapman RW, Chazouillère O, Invernizzi P, Jones DE, Lammert F, Parès A, Trauner M. EASL Clinical Practice Guidelines: Management of cholestaticliver diseases. European Association for the Study of the Liver. J. Hepatol 2009; 51:237-67.

17. Ina Marie A, Guro T, Benedicte A L, Boberg KM , Tom H K, Johannes R H. Effects of Coffee consumption, Smoking, and Hormones on Risk for Primary Sclerosing Cholangitis. Clin Gastroenterol Hepatol. 2014; 12(6):1019-28.

18. Levy C, Lindor KD. Primary sclerosing cholangitis: epidemiology, natural history, and prognosis. Semin Liver Dis. 2006; 26:22-30.

19. Okolicsanyi L, Fabris L, Viaggi S, Carulli N, Podda M, Ricci G. Primary sclerosing Cholangitis: clinical presentation, natural history and prognostic variables: an Italian multicentre study. The Italian PSC Study Group. Eur J Gastroenterol Hepatol 1996; 8:685-91.

20. Bergquist A, Glaumann H, Lindberg B, Broome U. Primary sclerosing cholangitis (PSC) can present with acute liver failure: Report of two cases. J Hepatol 2006; 44:1005-08.

21. Gohlke F, Lohse AW, Dienes HP, Lohr H, Marker-Hermann E, Gerken G,

Buschenfelde KMZ. Evidence for an overlap syndrome of autoimmune hepatitis and Primary sclerosing cholangitis. J Hepatol 1996; 24:699-705.

22. Bjornsson E, Chari ST, Smyrk TC. Immunoglobulin G4 associated cholangitis: description of an emerging clinical entity based on review of the literature. Hepatology 2007; 45:1547-54.

23. Kalaitzakis E, Levy M, Kamisawa T, Johnson GJ, Baron TH, Topazian MD, Takahashi N, Kanno A, Okazaki K, Egawa N, Uchida K, Sheikh K, Amin Z, Shimosegawa T, Sandanayake NS, Church NI, Chapman MH, Pereira SP, Chari S, Webster GJM. Endoscopic retrograde cholangiography does not reliably distinguish IgG4-associated cholangitis from primary sclerosing cholangitis or cholangiocarcinoma. Clin Gastroenterol Hepatol. 2011; 9:800-03.

24. Chapman R, Fevery J, Kaloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ. Diagnosis and management of primary sclerosing cholangitis. Hepatology 2010; 51:660-78.

25. Hay JE, Lindor KD, Wiesner RH, Dickson ER, Krom RA, LaRusso NF. The metabolic bone disease of primary sclerosing cholangitis. Hepatology 1991; 14:257-61.

26. Broomé U, Olsson R, Lööf L, Bodemar G, Hultcrantz R, Danielsson A, Prytz H, Sandberg-Gertzén H, Wallerstedt S, Lindberg G. Natural history and prognostic factors in 305 Swedish Patients with primary sclerosing cholangitis. Gut 1996; 38:610-15.

27. Wiesner RH, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, Fleming TR, Fisher LD, Beaver SJ, Larusso NF. Primary sclerosing cholangitis: The natural history, prognostic factors, and survival analysis. Hepatology 1989; 10:430-36.

28. Kim WR, Therneau TM, Wiesner RH, Poterucha JJ, Benson JT, Malinchoc M,

LaRusso NF, Lindor KD, Dickson ER. A revised natural history model for Primary sclerosing cholangitis. Mayo Clin Proc. 2000; 75(7):688-94.

29. Mendes FD, Jorgensen R, Keach J, Katzmann JA, Smyrk T, Donlinger J, Chari S, Lindor KD. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am J Gastroenterol 2006; 101:2070-75.

30. Toosi MN, Heathcote J. Pancreatic pseudotumor with sclerosing pancreato-cholangitis: is this a systemic disease? Am J Gastroenterol 2004; 99:377-82.

31. Zen Y, Harada K, Sasaki M. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol 2004; 28:1193-1203.

32. Fulcher AS, Turner MA, Franklin KJ, Shiffman ML, Sterling RK, Luketic VA, Sanyal AJ. Primary sclerosing cholangitis: evaluation with MRI cholangiography - a case-control study. Radiology 2000; 215:71-80.

33. Khan AN, Macdonald S, Sheen AJ. Primary sclerosing cholangitis imaging [Internet]. 2017 [cited 10 May 2017]. Available from: http://emedicine.medscape.com/article/365202-overview.

34. PSC – MRCP [Internet]. 2017 [cited 11 July 2017]. Available from: http://imgarcade.com/primary-sclerosing-cholangitis-mrcp.html.

35. van de Meeberg PC, Portincasa P, Wolfhagen FH, van Erpecum KJ, VanBerge-Henegouwen GP. Increased gall bladder volume in primary sclerosing cholangitis. Gut 1996; 39:594-99.

36. Levy AD. Biliary Ducts – pathology, PSC with thickening of the wall of bile duct. [Internet]. 2017 [cited 23 July 2017]. Available from: http://www.radiologyassistant.nl/en/p49e17de25294d/biliary-ducts-pathology.html

37. Steele IL, Levy C, Lindor KD, Primary Sclerosing Cholangitis - Approach to Diagnosis [Internet]. 2017 [cited 13 August 2017]. Available from: http://www.medscape.com/viewarticle/552500_6

38. Pernick N, Thakore S**.** Ig-G4 cholangitis [Internet]. 2017 [cited 19 August 2017]. Available from: http://pathologyoutlines.com/caseofweek/case351.htm.

39. Cameron JL, Pitt HA, Zinner MJ, Herlong HF, Kaufman SL, Boitnott JK, Coleman J. Resection of hepatic duct bifurcation and transhepatic stenting for sclerosing cholangitis. Ann Surg 1988; 207:614-22.

40. Farges O, Malassagne B, Sebagh M, Bismuth H. Primary sclerosing cholangitis: liver transplantation or biliary surgery. Surgery 1995; 117:146-55.

41. Choi CH, Jung SA, Lee BI, Lee KM, Kim JS, Han DS. Diagnostic guideline of ulcerative colitis. Korean J Gastroenterol 2009; 53:145-160.

42. Ye BD, Jang BI, Jeen YT, Lee KM, Kim JS, Yang SK. Diagnostic guideline of Crohn's disease. Korean J Gastroenterol 2009; 53:161-176.

43. Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002; 347:417-429.

44. Jenkins D, Balsitis M, Gallivan S. Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease. The British Society of Gastroenterology Initiative. J Clin Pathol 1997; 50:93-105

45. Goldman H. Colonic biopsy in the inflammatory bowel disease. Surg Pathol 1991; 4:3-24

46. Seldenrijk CA, Morson BC, Meuwissen SGM. Histopathological evaluation of colonic mucosal biopsy specimens in chronic inflammatory bowel disease: diagnostic implications. Gut 1991; 32:1514-1520

47. Molodecky NA, Kareemi H, Parab R, Barkema HW, Quan H, Myers RO, Kaplan GG. Incidence of primary sclerosing cholangitis: A systematic review and meta-analysis. Hepatology 2011; 53(5):1590.

48. Lindor KD, Kowdley KV, Harrison ME. ACG Clinical Guideline: Primary sclerosing cholangitis. American College of Gastroenterology. Am J Gastroenterol 2015; 110(5): 646-59; quiz 660.

49. Elaine T, Sripriya B, Carlo S, ChinShang L, Christopher LB. The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population. BMC Gastroenterology 2011; 11:83.

50. Nicholas F, Benjamin L, Shneider L, Gores GJ, James SP, Doo E, Hoofnagle JH. Primary sclerosing cholangitis: Summary of a workshop. Hepatology 2006; 44(3): 746-64.

51. Koczka CP, Geraldino-Pardilla LB, Garrett LG, Primary sclerosing cholangitis and its relationship to the colon in a black cohort of inflammatory bowel disease patients. J Clin Gastroenterol 2014; 48:19-21.

52. Kelly P, Patchett S, McCloskey D, Alstead E, Farthing M, Fairclough P. Sclerosing cholangitis, race and sex. Gut 1997; 41(5):688-89.

53. Sano H, Nakazawa T, Ando T, Hayashi K, Naitoh I, Okumura F, Myiabe K, Yoshida M, Takahashi S, Ohara H, Joh T. Clinical characteristics of inflammatory Bowel disease associated with primary sclerosing cholangitis. J Hepatobiliary Pancreat Sci. 2011; 18 (2):154-61.

54. Buchel OC, Bosch FJ, Janse van Rensburg J, Bezuidenhout E, de Vries CS, van Zyl JH, Middlecote BD, de K Grundling H, Fevery J. Primary sclerosing cholangitis, Crohn's disease and HLA-B27 in black South African women. Gastroenterol 2012; 75(4):454-57.

55. Ina Marie A, Guro T, Benedicte AL, Kirsten MB, Tom HK, Johannes RH. Effects of Coffee Consumption, Smoking, and Hormones on Risk for Primary Sclerosing Cholangitis Clinical. Gastroenterology and Hepatology 2014; 12:1019-28.

56. Harrison PM. Diagnosis of Primary Sclerosing Cholangitis. Journal of Hepato-Biliary-Pancreatic Surgery 1999; 6(4):356-60.

57. Mordechai R, Judith S. Gavaler R, Schade VJ, Dindzans M, Chien D, Van Thiel H. Does primary sclerosing cholangitis occurring in association with inflammatory bowel disease differs from that occurring in the absence of inflammatory bowel disease? Journal of Hepatology 1990; 11(1):7-11

58. Yanai H, Matalon S, Rosenblatt A, Awadie H, Berdichevski T, Snir Y, Kopylov U, Katz L, Stein A, Mlynarsky L, Tulchinsky H, Konikoff FM, Horin SB, Braun M, Ben-Ari Z, Chowers Y, Baruch Y, Shibolet O, Dotan I. Prognosis of primary sclerosing Cholangitis in Israel is independent of coexisting inflammatory bowel Disease. J Crohns Colitis 2015; 9:177-84.

59. Ngu JH, Gearry RB, Wright AJ, Stedman CA. Inflammatory bowel disease is Associated with poor outcomes of patients with primary sclerosing cholangitis. Clin

Gastroenterol Hepatol 2011; 9:1092-97.

60. Edwards CN, Griffith SG, Hennis AJ, Hambleton IR. Inflammatory bowel disease: incidence, prevalence, and disease characteristics in Barbados, West Indies. Inflamm Bowel Dis. 2008; 14:1419–24.

61. Marelli L, Xirouchakis E, Kalambokis G, Cholongitas E, Hamilton M, Burroughs A. Does the severity of primary sclerosing cholangitis influence the clinical course of associated ulcerative colitis? Gut 2011; 60 (9):1224-28.

62. Zheng HH, Jiang XL. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a meta-analysis of 16 observational studies. Eur J Gastroenterol Hepatol 2016; 28:383-90.

63. Textor HJ, Flacke S, Pauleit D, Keller E, Neubrand M, Terjung B, Gieseke J, Scheurlen C, Sauerbruch T, Schild HH. Three-dimensional magnetic Resonance cholangiopancreatography with respiratory triggering in the diagnosis of Primary Sclerosing cholangitis: comparison with endoscopic retrograde Cholangiography. Endoscopy 2002; 34:984-90.

64. Worthington J, Chapman R. Primary sclerosing cholangitis. Orphanet J Rare Dis. 2006; 1:41.

65. Yiman K, Bowlus C, Diagnosis and classification of primary sclerosing cholangitis. Autoimmune REV. 2014; 13:445-50.

66. Tamir Miloh, Pinar Bulut. Primary Sclerosing Cholangitis during childhood and Adolescence. CLD Journal. 2013; 2:215-18.

67. O' Toole A, Alakkari A, Keegan D, Doherty G, Mulcahy H, O'donoghue D. Primary sclerosing cholangitis and disease distribution in inflammatory bowel disease. Clin Gastroenerol Hepatol 2012; 10:439-41.

68. Befeler AS, Lissoos TW, Schiano TD, Conjeevaram H, Dasgupta KA, Millis JM, Newell KA, Thistlethwaite JR, Baker AL. Clinical course and management of Inflammatory bowel disease after liver transplantation. Journal of Transplantation 1998; 65:393-96.

69. Loftus EV Jr, Sandborn WJ, Tremaine WJ, Mahoney DW, Zinsmeister AR,

Offord KP, Melton LJ. Primary Sclerosing Cholangitis Is Associated With Non-smoking: A Case-Control Study. Gastroenterology 1996; 110:1496-1502.

70. Porayko MK, Wiesner RH, LaRusso NF, Ludwig J, MacCarty RL, Steiner LB, Twomey CK, Zinsmeister AR. Patients with asymptomatic primary sclerosing cholangitis frequently have progressive disease. Gastroenterology 1990; 98:1594-1602.

Appendix A: Data Collection Sheet

1.0 Study Number
2.0 Age
3.0 Gender
- 3.1 Male
- 3.2 Female

4.0 Ethnicity
- 4.1 Black African
- 4.2 White
- 4.3 Asian
- 4.4 Coloured

5.0 Smoking
6.0 Socio-economic status
7.0 PSC
- 7.1 No
- 7.2 Yes
  - 7.2.1 Age at diagnosis
  - 7.2.2 Duration
  - 7.2.3 Family history
  - 7.2.4 Clinical findings
  - 7.2.5 Associated liver disorders

8.0 IBD
- 8.1 No
- 8.2 Yes
  - 8.2.1 Type
    - 8.2.1.1 Ulcerative Colitis
    - 8.2.1.2 Crohns Disease
  - 8.2.2 Age at diagnosis
  - 8.2.3 Duration
  - 8.2.4 Extra GI manifestations
  - 8.2.5 Family history
  - 8.2.6 Extent of GI involvement

9.0 Blood results

9.1 Full blood count
9.2 Liver function test
9.3 INR
9.4 Inflammatory markers
9.5 CMP
9.6 Lipid profile
9.7 Viral screen

10.0 Autoimmune profile
11.0 Imaging
11.1 US
11.2 MRCP
11.3 ERCP
12.0 Liver biopsy
13.0 Surgery (liver transplantation)
14.0 Outcome

Appendix B: Ethics Clearance Certificate

R14/49 Dr Mohamed Alshmandi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140874

NAME: (Principal Investigator)	Dr Mohamed Alshmandi
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johanesburg Academic Hospital
PROJECT TITLE:	Primary Sclerosing Cholangitis (PSC) in a Cohort of Black Southern African Patients
DATE CONSIDERED:	29/08/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Adam Mahomed and Alison Bentley
APPROVED BY:	Professor P Cleaton-Jones, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/09/2014

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 _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Protocol Approval form

Faculty of Health Sciences
Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

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

29 September 2014
Person No: 871119
PAG

Dr MA Alshmandi
269 Jewel Avenue
Flat 1 Lenasia
Extension 13
1827
South Africa

Dear Dr Alshmandi

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Primary sclerosing cholangitis (PSC) in a cohort of Black Southern African patients.* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences