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Clinicopathological presentation of liver abscesses at two Johannesburg Academic Hospitals

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Clinicopathological presentation of liver abscesses at two Johannesburg Academic Hospitals

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UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Masters of Medicine

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DECLARATION

I, Krevosha Pillay (student number 2005441), declare that this research report is my unaided work. It is being submitted for the degree of Masters of Medicine in Surgery at the University of Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any other degree or examination at any other University.

This report was written according to the manuscript guidelines of the World Journal of Gastroenterology (https://www.wjgnet.com/bpg/GerInfo/200) and is presented in the submissible format for MMed reports by the Faculty of Health Sciences of the University of Witwatersrand.



2023/05/18

DEDICATION

I dedicate this thesis to my parents, Lalitha and Brian Pillay, my sisters Nivashini, Melisha and Kreshona, and my partner Gerhard Coetzee for their unwavering belief in me and for their support throughout my endeavour of becoming a surgeon.

PRESENTATIONS ARISING FROM THIS STUDY

This research was presented at:

1. The Department of General Surgery Academic meeting, March 2022
2. Bert Myburg Research Forum, Department of Surgery, University of the Witwatersrand, Johannesburg, November 2022

ABSTRACT

Background: Hepatic abscesses represent infection of the liver parenchyma from bacteria, fungi and parasitic organisms. Trends in both the microbiology and management of these have changed over the past decade. There is a paucity of published data regarding the clinicopathological features of liver abscesses in South Africa and Africa.

Aims: To evaluate the demographic, clinical, radiological and laboratory presentations of liver abscesses at two University of Witwatersrand referral institutions.

Methods: Review and analysis of information accessed from electronic discharge summaries (EDS) of patients from two hepatopancreatobiliary (HPB) tertiary units in Gauteng, from January 2016 to December 2020. All patients older than 13 years, presenting with liver abscesses: pyogenic, amoebic and hydatid, were included. Clinical findings, laboratory, microbiology and radiology results were collated and analysed.

Results: There were 222 patients: 123 males (55.41%) and 99 females (44.59%), with a median age of 48 years. HIV (24.23%), hypertension (20.57%) and diabetes mellitus (16.83%) were the main comorbidities observed. The majority (74.77%) of abscesses were pyogenic, while amoebic and hydatid abscesses represented 16.22% and 9.01%, respectively. The predominant aetiology of the pyogenic liver abscesses (PLA) was biliary. White cell count (WCC) and CRP were significantly higher in the pyogenic group ($p < 0.0002$ and $p < 0.007$, respectively) as compared to the amoebic and hydatid groups. In patients with PLAs, organisms were cultured on blood (17.58%) and abscess fluid (56.6%). *Klebsiella*, *Escherichia coli* and *Streptococci* were the most cultured organisms. Sixteen percent of the cultures were polymicrobial. Seventy-six percent of patients requiring drainage had a percutaneous drain placed, while 8.76% required open surgery. The median length of hospital stay was 13 days. There was a mortality rate of 3.02%.

Conclusions: In this study, the commonest type of liver abscess was PLAs in middle-aged males. The microbiology was similar to Asian populations and non-surgical management via percutaneous drainage was sufficient in the majority of cases. Uniquely, HIV occurred in about one-quarter of the group and was significantly higher in the amoebic and hydatid groups.

Whilst this did not impact outcomes, further prospective studies are required to ascertain the impact of HIV in these patients.

Key Words: Amoebic liver abscess, Hydatid liver disease or Liver Echinococcosis, HIV, Pyogenic liver abscess, Percutaneous drainage

Core Tip*:*

The incidence, aetiology and microbiology of liver abscesses vary across geographical areas. There is a paucity of published data evaluating the characteristics of liver abscesses in South Africa and other low- and middle-income countries (LMICs) in Africa. This study showed a predominance of pyogenic liver abscesses in middle-aged males. HIV and diabetes mellitus were major co-morbidities noted across all groups, highlighting immunosuppression as an important factor in the pathogenesis of infective liver collections. HIV comorbidity in patients with liver abscesses is not well documented in the literature and was the most common comorbidity in all groups. The microbiology of pyogenic collections is similar to that of Asian populations, with *Klebsiella* as the predominant isolate. The majority of patients were managed non-operatively, with surgery reserved for complications. The small number of hydatid disease in this study makes it difficult to draw significant conclusions in this group of patients, and further prospective studies are required.

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LIST OF ABBREVIATIONS

AKI – acute kidney injury

ALP – alkaline phosphatase

AST- aspartate aminotransferase

ALT- alanine aminotransferase

CBD – common bile duct

CHD – common hepatic duct

CHBAH – Chris Hani Baragwanath Academic Hospital

CMJAH – Charlotte Maxeke Johannesburg Academic Hospital

CRP – C-Reactive protein

CT – computed tomography

DVT – deep vein thrombosis

EDS – electronic discharge summaries

ERCP – endoscopic retrograde cholangiopancreatography

GGT – gamma-glutamyl transferase

HIV – Human Immunodeficiency Virus

ICU – intensive care unit

IQR – interquartile range

INR – international normalised ratio

LMIC – low and middle-income countries

MRI – magnetic resonance imaging

PAIR – puncture, aspiration, injection, re-aspiration

PE – pulmonary embolism

PLA – pyogenic liver abscesses

NHLS – National health laboratory services

WCC – white cell count

1. INTRODUCTION

Liver abscesses represent a suppurative infection of the hepatic parenchyma from bacteria (pyogenic), parasites and rarely fungi (1,2). Mixed aetiology can occur with bacterial superinfection of a parasitic abscess. Pyogenic liver abscesses (PLAs) remain the most common in the developed world (1). The incidence differs across population groups and geographic areas. In North America, an incidence of 3.6 per 100,000 has been reported (3), whilst in Canada, the incidence increased from 2.3 to 3.7 per 100,000 individuals over a 10-year period (4). In the east, incidences are as high as 17.6 per 100,000 individuals (5). The maximum incidence appears to be between the ages of 50 – 70 years, with a male predominance (6,7). Amoebic liver abscesses caused by *Entamoeba histolytica* (*E. histolytica*) are more common in developing countries like India and Mexico (1,8,9). Echinococcosis, or hydatid disease, is caused by the tapeworm belonging to the genus *Echinococcus*. Hepatic echinococcosis is caused by infection with the species *Echinococcus granulosis* (cystic echinococcosis) and *Echinococcus multilocularis* (alveolar echinococcosis) (10,11). Cystic echinococcosis is largely a neglected and understudied parasitic zoonosis in the literature, but it is an important disease worldwide.

There are definite distinctions between the microbiology, demographic characteristics and clinical behaviour noted in different geographical areas and population groups between the above hepatic infections (12). The understanding of disease factors and the microbiological agents associated with liver abscesses is vital as it has direct implications for treatment. Management options are antibiotics alone or combined with drainage procedures. The trend in management has shifted from open surgical drainage to radiologically guided percutaneous drainage. Percutaneous drainage, either ultrasound-guided or computed tomography (CT) scan-guided, has become the most common approach (13,14). Surgery is reserved for failed percutaneous drainage or to manage complications and rupture (12).

There is a paucity of published data evaluating the characteristics of liver abscesses in South Africa. González-Alcaide et al. (9) analysed the research on liver abscesses and found that the United States, Japan and Taiwan were the largest contributors to research in this field. Most papers on amoebic abscesses were from India and Mexico (9). South Africa has a high burden of HIV comorbidity, and whilst immunosuppression and diabetes mellitus have been implicated in the pathogenesis of liver abscesses (15), there is very little data to evaluate the impact of HIV on presentation and outcome.

This study is a retrospective analysis to evaluate demographic, clinical, radiological and laboratory presentations of liver abscesses in South Africa. The secondary objectives were to describe the management modalities, outcomes, and impact of HIV and non-HIV co-morbidities on presentation and outcomes.

2. METHODS

This is a descriptive study analysing retrospective data on patients with liver abscesses admitted to the study sites from January 2016 – December 2020. The University of the Witwatersrand Human Research Ethics Committee (Medical) approved the study (M200245).

2.1. Study Population

Patients presenting with pyogenic and amoebic liver abscesses and hydatid liver disease at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) were included. These two hospitals are tertiary-level referral centres and also serve primary and secondary-level patients. The study covered a 5-year period from 01 January 2016 to 31 December 2020. All patients presenting with pyogenic and amoebic liver abscesses and patients with hydatid liver disease were included. Patients were identified using the hospitals' electronic discharge summary (EDS) database identifying the ICD 10 codes: K75.0 (Abscess of the liver), A06.4 (Amoebic liver abscess) and K77.0 (Liver disorders in infectious and parasitic diseases classified elsewhere). Ward admission records were also screened for patients that may have been missed. Patients under 13 years of age, patients with recurrent admission, and abscesses secondary to trauma were excluded.

The information from the summaries was cross-referenced with National Health Laboratory Service (NHLS) records and participating hospitals' radiology records. Relevant datasets were captured on an excel data sheet. The data recorded included demographic characteristics, co-morbidities, clinical presentation, laboratory results, radiology findings, treatment modalities, complications and mortalities. The results of blood tests (including blood cultures) were from specimens obtained on admission. The results of abscess cultures were from specimens taken at the time of percutaneous or surgical drainage. Amoebic and hydatid serologies, histology findings and imaging characteristics were used to differentiate types of infective liver collections. The aetiology of pyogenic liver abscesses was divided into groups according to the presumed source of infection: biliary causes (cholecystitis, cholangitis from benign or malignant biliary tract disease); portal pyaemia (haematogenous spread via the portal vein from an infectious intra-abdominal process); haematogenous (from a distant infective process); cryptogenic (where no cause could be identified) and other (intra-abdominal malignancy). The management modalities evaluated were the type of antibiotic used, the need and method of drainage (percutaneous versus surgical) and the use of endoscopic retrograde cholangiopancreatography (ERCP). Mortality was defined as death during hospital admission.

2.2. Statistical analysis

Data analysis was performed using STATA ® statistical software version 16. Descriptive statistics were performed for continuous variables and expressed as mean and standard deviations or median and interquartile ranges for variables that were not normally distributed. Categorical variables were expressed as percentages. The differences between groups and mortality data were evaluated by the Mann-Whitney test and one-way ANOVA, with p-values of <0.05 considered statistically significant.

3. RESULTS

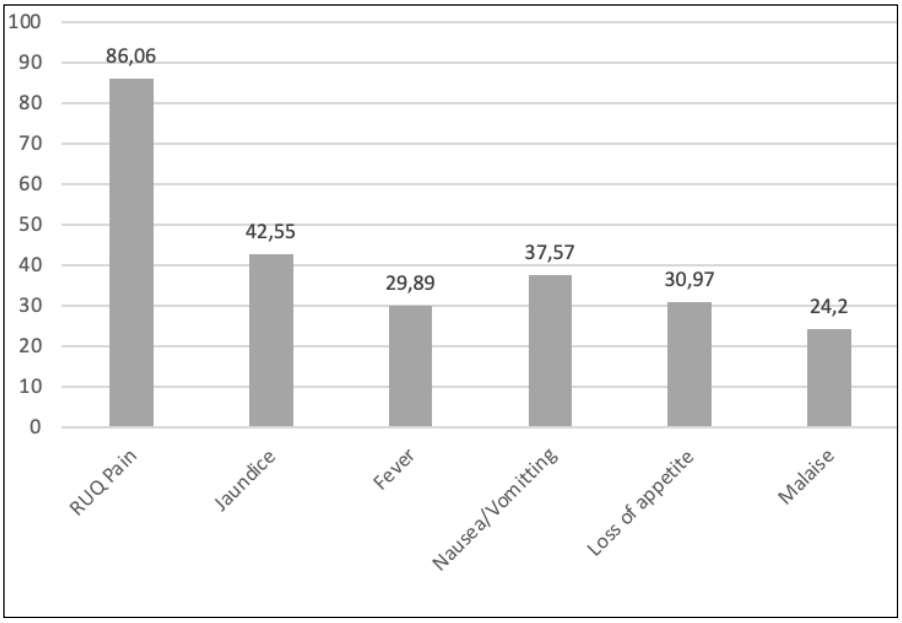
3.1. Demographics, comorbidities and clinical presentation

Two hundred and twenty-two (222) patients met the inclusion criteria for the study. The median age was 48 years (range 15 - 87 years). Fifty-five percent (n=123) of patients were males. The most common comorbidity found in the cohort was HIV (24.63%), followed by hypertension (22.73%) and diabetes mellitus (17.27%). Nineteen patients had an unknown HIV status and were not tested during the hospital admission. One patient had documented cirrhosis and one had chronic kidney disease. Table 1 illustrates the differences in demographics between the types of liver abscesses. Hydatid and amoebic pathologies present at a significantly younger age (p=0.0005) and with a female predominance in hydatid disease (p=0.001). Regarding comorbidities, HIV was more common in the amoebic and hydatid subgroups, with diabetes mellitus more common in the pyogenic group. Presenting symptoms included right upper quadrant pain (86.08%), jaundice (42.55%), nausea and vomiting (37.97%), and loss of appetite (32.17%) (Figure 1). Fever was present in 28.89% of patients and more frequently in the pyogenic and amoebic groups than in the hydatid group.

Table 1: Differences in demographics between types of liver collections

	Pyogenic (n =166)	**Amoebic (n=36)**	**Hydatid (n=20)**	**P-value**
Age	52 (41 – 60)	45.5 (35.5 – 55.5)	38.5 (26 – 44)	0.0005
Gender				
Male (*n*, %)	90 (54.22)	28 (77.78)	5 (25)	0.001
Female (*n*, %)	76 (45.78)	8 (22.76)	15 (75)	0.001
HIV positive (*n*,%)	27 (17.88)	15 (45.45)	8 (42.11)	0.001
Diabetes mellitus (*n*,%)	35 (21.34)	2 (5.56)	1 (5)	0.024

Figure 1: Presenting symptoms observed in the patient population



3.2. Types of abscesses and aetiology

Pyogenic liver abscesses comprised 74.77% (n=166) of the study population. Sixteen percent (n=36) of patients were diagnosed with amoebic abscesses and 9% (n=20) with hydatid disease. One patient was diagnosed with a fungal abscess with actinomycosis confirmed on liver biopsy and was excluded from further statistical analysis. The aetiology of PLA was of biliary origin in 48.8% (n=81). These were related to malignancy in 13.25% (n=22), benign biliary disease in 25.3% (n=42) and due to biliary interventions in 10.25% (n=17) of patients. The most common benign biliary cause was due to choledocholithiasis, which was diagnosed in 23 patients. Intra-abdominal causes via portal seeding contributed to 8.43%, with appendicitis noted most frequently (n=7). In 39.16% (n=65) of cases, there was no identifiable cause (cryptogenic abscess). (Table 2)

Table 2: Aetiology of pyogenic abscesses

Disease	n=166	%
Biliary	**81**	**48.80**
Benign	42	25.30
Benign CBD/CHD stricture	8	4.82
Cholecystitis/complicated cholecystitis	6	3.61
Choledocholithiasis	23	13.86
Mirrizi syndrome	3	1.81
HIV Cholangiopathy	1	0.60
Ruptured gallbladder (sickle cell crisis)	1	0.60
Malignant	22	13.25
Cholangiocarcinoma	7	4.22
Gallbladder cancer	6	3.61
Pancreatic cancer	5	3.01
Periampullary tumour	4	2.41
Iatrogenic injury/biliary intervention	17	10.24
Bile duct injury (laparoscopic cholecystectomy)	2	1.20
Bile duct stricture (laparoscopic cholecystectomy)	2	1.20
Bile duct stricture (post pancreaticoduodenectomy)	1	0.60
Benign stricture (blocked stent)	2	1.20
Choledocholithiasis (blocked biliary stent)	2	1.20
Biliary Malignancy (blocked stent)	7	4.22
Post portal vein embolisation (cholangiocarcinoma)	1	0.60
Portal Pyaemia	**14**	**8.43**
Appendicitis	7	4.22
Colitis	2	1.20
Diverticular disease	3	1.81
Perforated peptic ulcer	1	0.60
Jejunal perforation	1	0.60
Other	**5**	**3.01**
Locally advanced colon cancer	1	0.60
Metastatic colon cancer	2	1.20
Metastatic adenocarcinoma (unknown primary)	1	0.60
Rectosigmoid stricture	1	0.60
Haematogenous	**1**	**0.60**
Cryptogenic	**65**	**39.16**

3.3. Laboratory Investigations and Microbiology

The laboratory results differed across the groups by pathology (Table 3). The pyogenic group had a raised median white cell count (WCC) and C-reactive protein (CRP), which was significantly higher than the amoebic and hydatid groups. Seventy-five percent of patients with PLA had a leucocytosis, 98.08% had a raised CRP and 21.02% had a CRP above 300mg/L (Table 4). The median total bilirubin was mildly elevated in the pyogenic group and within the normal range for the amoebic and hydatid collections. Fifty-four percent of patients with PLAs had hyperbilirubinemia. Regarding liver enzymes, the ductal enzymes were raised in all three groups. In patients with a PLA larger than 10 cm, the median WCC, CRP, total bilirubin, alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) was higher than the overall median values for PLAs, however, this was not statistically significant. Blood cultures were obtained in 54.81% (n=91) of patients presenting with PLA and 17.58% (n=16) were positive. The most commonly isolated organism was *Escherichia coli (E. coli*) (41.11%; n=7), followed by *Klebsiella pneumoniae* (29.41%; n=5). One hundred and six patients had aspirates sent for microbiological analysis, of which 56.6% (n=60) were positive. *Klebsiella* species (n=28) (*pneumoniae, oxytoca* and *species*) and *E. coli* (n=13) were cultured most frequently (46.67% and 21.67%, respectively). Other organisms cultured were *Streptococci* (18.3%; n=11) and *Enterococci* (18.3%; n=11). Seventeen of the abscess aspirates (16.03%) were polymicrobial. In the patients with amoebic abscesses and hydatid disease, 11 patients had superimposed bacterial infection with positive aspirates in 7 and 4 patients, respectively.

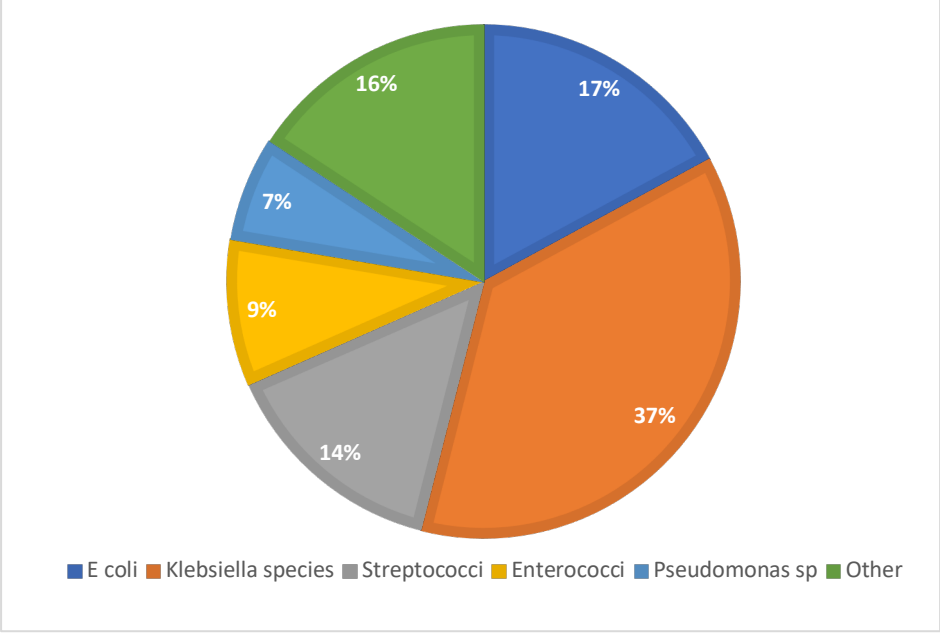
Table 3: Biochemical measurements according to abscess type

	Pyogenic		Amoebic		Hydatid		
Laboratory Test	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**P-value**
WCC (4 – 10 x 10^9/L)	15.76	9.9 – 21.2	13.18	9.16 – 16.02	8.90	6.28 – 12.76	0.0002
CRP (<10 mg/L)	211	110 – 289	181	60.5 – 246.5	90	28.5 – 215.5	0.007
Haemoglobin (12 – 15 g/dL)	10.5	8.8 – 12.1	10.5	8.8 – 11.9	11.35	8.35 – 12.35	0.83
Platelets (150 – 400 x 10^9/L)	391	242 – 575	495	401 – 615.5	483.5	322.5 – 562.5	0.02
Albumin (35 – 50 g/L)	29	25 – 34	28	24 – 32	32.5	26.5 – 40.5	0.11
Total Bilirubin (5 – 21 umol/L)	23	11 – 80	9	5 – 19	7.5	6 – 29.5	0.0001
Conjugated Bilirubin (<3 umol/L)	16	6 – 52	4	3 – 14	4.5	3 – 21.5	0.0001
ALT (7 – 35 U/L)	39	25 – 89	26	12 – 44	20.5	14 – 32	0.0002
AST (13 – 35 U/L)	48	27 – 87	32	20 – 63	31.5	23.5 – 40.5	0.008
ALP (42 – 98 U/L)	221	169 – 425	179	124 – 243	215	120 – 421	0.01
GGT (<40 U/L)	201	110 – 416	157	82 – 208	130	93 – 315.5	0.03
Urea (2.1 – 7.1 mmol/L)	5.2	3.2 – 9.8	3.6	2.7 – 5	3.7	3.1 – 6.1	0.02
Creatinine (49 – 90 mmol/L)	79	59 – 117.5	67	58 – 88	66.5	50 – 74	0.02
INR (0.9 – 1.2)	1.31	1.18 – 1.49	1.27	1.21 – 1.46	1.2	1.14 – 1.43	0.5

Table 4: Laboratory findings outside the normal range in patients presenting with pyogenic liver abscesses

Parameters	No of patients	%
Leucocytosis	121	74.69
Raised CRP (>10 mg/L)	154	98.09
CRP (>300 mg/L)	33	21.02
Thrombocytopenia	18	12.02
HB (<10 g/dL)	65	40.63
Hypoalbuminaemia (<30 g/L)	89	55.97
Bilirubin (>21 umol/L)	85	53.46
ALT (>2 x normal)	44	28.03
AST (>2 x normal)	53	33.76
ALP (>2 x normal)	94	58.75
GGT (>2 x normal)	132	82.50
INR >1.5	29	22.83

Figure 2: Pie chart of the organisms cultured from abscess aspirates



3.4. Imaging Characteristics

The imaging modalities used to diagnose all abscesses were primarily ultrasound and computed tomography (CT) scans. MRI was used to further characterise lesions, ascertain aetiology and determine communication with the biliary tree. The median size of PLA was 8 cm, with 76.79% being larger than 5 cm. The predominant radiological presentation for all groups was multiple collections on the right side of the liver, however, amoebic and hydatic collections were significantly larger.

Table 5: Imaging characteristics and management modalities of infective liver collections

	Pyogenic	**Amoebic**	**Hydatid**	P-**value**
Ultrasound (*n,*%)	125 (79.11)	25 (78.13)	15 (72.22)	
CT (*n,*%)	146 (90.12)	30 (90.91)	17 (94.44)	
MRI (*n,*%)	13 (8.13)	0	2 (11.11)	
Size (Median; IQR)	8 cm (5.85 – 10)	11 cm (9 – 14)	14.5 cm (12 – 19.3)	0.0001
Range	1.5 cm – 25 cm	4.5 cm – 25 cm	3 cm – 22 cm	
Size >5 cm (*n,*%)	86 (76.79)	16 (84.21)	9 (90)	
Multiple (*n,*%)	80 (51.28)	15 (46.88)	8 (47.06)	
Right (*n,*%)	54.89	52.17	50	
Left (*n,*%)	25.56	13.04	21.43	
Bilobar (*n,*%)	19.55	34.78	28.57	
Percutaneous drainage	120 (74.53)	30 (90.91)	8 (42.11)	
ERCP	50 (31.25)	4 (12.12)	9 (45.00)	
Surgery	6 (3.73)	5 (13.89)	9 (45)	
PAIR*			2 (10.53)	

*Puncture, Aspiration, Injection, Re-aspiration

3.5. Management

To manage these patients, various anti-microbial regimens were used depending on the type of abscess. In the pyogenic group, amoxicillin-clavulanic acid and piperacillin-tazobactam were the empiric antibiotics started in most instances and then tailored to the culture results based on susceptibility testing. The antimicrobial used for amoebic collections was metronidazole, whilst albendazole was used for hydatid disease. Percutaneous intervention was used in 74.18% (n = 158) of cases. Percutaneous methods included aspiration alone (n=2), and percutaneous

catheter drainage (73.24%, n=156). Pyogenic liver abscesses required percutaneous intervention in 74.09% (n=123) of instances and surgical management in 3.73% (n=6). Thirty-seven patients with PLA did not require drainage. The median size of PLAs not requiring drainage was 5.15 cm and the median size of abscesses requiring drainage was 8.2 cm. Thirty-one percent of patients underwent an ERCP (n=50). ERCP was used in PLAs to treat benign and malignant biliary tract obstruction. In the amoebic group, ERCP and stenting were required in four patients due to a fistulous connection between the biliary tracts and the abscess cavity. In the hydatid group, nine patients required ERCP: two patients who developed postoperative bile leaks, one for obstructive jaundice secondary to a stricture, one for compression at the confluence of the hepatic ducts, three who had biliary fistulae and two who had diagnostic ERCPs.

The indications for surgical management in patients presenting with PLA was rupture (n=3) and two patients had an aspiration of their liver abscesses at the time of cholecystectomy. In the subgroup of patients with amoebic abscesses, three had laparotomies for rupture, one had a laparoscopic necrosectomy and one had laparoscopic drainage. In the hydatid disease cases, five patients were admitted for elective surgical procedures and four patients had surgical procedures for symptoms unresponsive to medical treatment. The surgical procedures included three open cystectomies, three pericystectomies, one laparoscopic drainage of an infected hydatid cyst and two partial hepatectomies. Two patients had a PAIR procedure (puncture, aspiration, injection, re-aspiration).

3.6. Outcomes

The median length of stay was 13 days (IQR 8 – 21). Overall, 12,61% (n=28) of patients had complications (Table 6). The complications associated with amoebic liver abscesses were rupture in 3 patients and one post-ERCP pancreatitis. In patients with cystic echinococcosis, three complications were noted. Two patients developed deep vein thrombosis and one patient had intra-thoracic rupture of the hydatid cyst. There were seven documented deaths with a mortality rate of 3.02%. Eighty-three percent (n=6) of the deaths were in the pyogenic group: two patients had biliary tract malignancies, one patient died postoperatively after the repair of a bile duct injury, one patient had complicated appendicitis, two patients had cryptogenic abscess and died from septic shock. One death occurred in a HIV-positive patient diagnosed with an actinomycotic abscess on liver biopsy who died in ICU with septic shock. Patients who

died were noted to be older, however, this did not reach statistical significance. The presence of HIV or diabetes mellitus as comorbidities in patients who died was not significantly higher than in patients who were alive. Furthermore, no statistical significance was noted in WCC, CRP, bilirubin levels, ALP, GGT, cultures, or length of stay.

Table 6: Complications of liver abscesses

General complications	***n***	**Complications of liver abscess**	***n***
AKI	3	Lung abscess (pleuro-biliary fistula)	1
Aspiration pneumonia	1	Ruptured liver abscess	6
Clostridium Difficile infection	1	**Procedure related complications**	
DVT	2	Caecal stump blowout	1
DVT/PE	1	Contrast induced nephropathy	1
PE	2	Post ERCP bleed	1
Pneumonia	1	Pneumothorax	2
Pleural effusion	2	Post ERCP pancreatitis	1
		Small bowel injury	1

4. DISCUSSION

Demographics

There are varied incidences and demographics of liver abscesses geographically and a paucity of data in the South African population. This study is consistent with other studies with a male predominance and a mean age at presentation of 52 years. In the literature, a higher mean age is noted for PLA in Asian (6), Australian (12) and European populations (16,17) with a mean age of 60 years. Meddings et al. (3) showed a higher risk of developing pyogenic liver abscesses (PLA) within the age groups of 50 – 64 and 65 – 85 years. In contrast, this study demonstrated PLA presentation in younger individuals. Pyogenic liver abscesses are likely to occur in middle age and older patients due to the higher incidence of co-morbidities such as diabetes mellitus, pancreaticobiliary and other malignancies (18). About 10% of the world's population is infected with *Entamoeba histolytic*a (19). The distribution of the disease varies, however, it is often seen in developing countries (2) and is more prevalent in tropical and subtropical climates (19). Amoebic liver abscesses are associated with low socioeconomic status as well as chronic alcoholism (2,8). Studies in India have shown a higher incidence of amoebic liver abscesses compared to pyogenic liver abscesses (PLA), with up to two-thirds of cases being due to amoebiasis (2). Amoebic abscesses present at a younger age (40 – 43 years) than PLAs (2,20). In South Africa, a median age of 39 was previously documented (21). This is in keeping with the results of this study. Cystic echinococcosis, caused by the larval stages of *E. granulosis* infection, is the most common type of hydatid disease (11). It is considered a rural and occupational disease since infection usually occurs with the handling of livestock or feeding dogs with viscera of livestock. An Italian study evaluating clinical and demographic characteristics of cystic echinococcosis noted a median age of 45 and a female predominance in their patient population (22). A lower median age was noted in this study and in keeping a female predominance, corroborating Kloppers et al. in Cape Town (23).

Risk factors

Various studies have postulated that host immunity may play a role in the pathogenesis of liver abscesses. Diabetes mellitus as a co-morbid condition has been noted to be prevalent in patients presenting with pyogenic liver abscesses (4,6,15,17,24). It may be a risk factor even in the absence of other risk factors (15). This is reflected in the subgroup analysis, which showed that 21.3% of PLA patients had diabetes mellitus compared to 17.2% in the group and 5.6% in the

amoebic and hydatid groups, respectively. Patients with PLA and diabetes mellitus have been shown to have a worse prognosis and higher rates of mortality (15). HIV causes immunosuppression and may predispose patients to develop liver abscesses and affect outcomes. Few studies exist that consider HIV as a risk factor for the development of liver abscesses. Ghosh et al. (2) reported 2% HIV positivity in their study (which included amoebic and PLAs), significantly lower than the 24.4% of patients noted in this study. In the subgroup analysis, this translated to 17.9% of patients with PLAs, 45.5% with amoebic abscesses and 42.1% of patients with hydatid disease that were HIV positive. This is higher than the prevalence of HIV in South Africa which was recorded at 12,7% in 2016. HIV co-morbidity has been noted to be 17.9% in an Italian series of patients with cystic echinococcosis (22), but this is reported to be higher in African population groups. A study in Cape Town reported 50% of patients having HIV co-infection, which was associated with complicated disease (23). Immunosuppression has been postulated to affect the clinical course of hydatid disease and is seen in patients with disseminated disease (25).

Clinical Presentation

The symptoms of pyogenic and amoebic liver abscesses are non-specific and diagnosis requires a high index of suspicion. Liver abscesses usually present with abdominal pain and fever and less commonly nausea, vomiting and weight loss (1,26). Infection with *E. granulosis* is initially asymptomatic. Symptoms develop due to the increasing size and number of cysts within the liver and pressure effects on surrounding organs (11). These symptoms include epigastric and right upper quadrant pain, nausea and vomiting. Most of the patients in this study presented with right upper quadrant pain, nausea, vomiting, and jaundice. These symptoms can be attributed to the large median size of collections across the groups and the finding of multiple abscesses in 40% of patients.

Aetiology

Numerous studies have shown that the aetiology of pyogenic liver abscesses has shifted in the last decade. Biliary diseases (6,12) have superseded portal pyaemia when a specific aetiology is identified. Cryptogenic abscesses, where no exact cause can be identified, are still the most common in many series (12,14,18). This study contrasts the literature, as biliary causes were noted in 48.8% of patients and cryptogenic abscesses in 39.1%. Losie et al. (4) showed a

significant decrease in cryptogenic causes of PLA and an associated increase in biliary aetiologies after a 15-year period in a Canadian population. Benign biliary causes related to gallstone disease and its complications increased over this period as well as the presence of malignant biliary tract disease (cholangiocarcinoma). In this study, benign biliary disease, including choledocholithiasis and other complications of gallstone disease, predominated too, and cholangiocarcinoma was the most diagnosed malignancy. This may reflect the incidence of gallstone disease in our population and the long waiting times for surgery in patients with symptomatic gallstones in the public hospital setting.

Laboratory findings

C- reactive protein has been measured in other studies, documenting raised CRP in all patients presenting with PLA and high mean CRP level (12). Patients in all three groups were noted to have hypoalbuminaemia, which also indicates a systemic inflammatory response. Anaemia was noted in all the groups, and in just over a third of patients with PLA the haemoglobin was less than 10 g/dL. Anaemia is a common finding in the literature (6,7), with mean haemoglobin noted to be 10.9 g/dL by Santos-Rosa et al. (7) and 11.8g/dL by Pang et al. (12). Derangements in liver function tests were observed in the various groups. A larger proportion of patients had raised ductal enzymes (ALP and GGT) as opposed to AST and ALT levels, and the median ALP and GGT were raised across the groups. Other studies of PLA and amoebic liver abscesses have reported similar findings (6,20,27). Pang et al. (12) showed that liver enzymes were elevated in about 70% of patients and the mean values for ductal enzymes were higher. Bilirubin levels were elevated in 50% of their patients (corroborating the findings of this study), with 13% of patients having clinically significant hyperbilirubinaemia. In the subgroup of patients with PLAs, abscesses larger than 10 cm were associated with higher inflammatory markers and worse derangements of the ALP and GGT values. Whilst this did not reach statistical significance, it may have clinical relevance by indicating the presence of larger abscesses.

Radiological Findings

As noted in the literature (12,17,24,26) and the foregoing, clinical and laboratory findings are non-specific. Diagnosis is aided by imaging techniques. Ultrasound remains an important diagnostic tool and with the addition of a CT scan, the diagnosis can be confirmed in 90% of

cases (1). The combination of imaging modalities allows for characterisation between liver abscesses and cystic echinococcosis and for specific aetiologies to be determined in the case of PLA (6,28). Larger collections were noted in the hydatid disease subgroup. This may reflect bias as a fair proportion of patients were admitted for elective surgery due to cyst sizes larger than 10 cm or due to pressure symptoms and pain. In all three subgroups, the collections were located on the right side of the liver. In the case of pyogenic collections, literature suggests that this is due to portal vein anatomy and a dense network of biliary canaliculi in the right lobe. This observation has been reported in other studies (14,17,28). Hydatid disease has also been found to predominate on the right side of the liver (29) and ultrasonographic features of amoebic abscesses are described as a solitary, well-defined cystic, intrahepatic cavity, most commonly found in the posterior part of the right lobe (2,19).

Microbiology

The cultures from aspirates had a higher positive bacterial yield than blood culture. This is in keeping with data from Pang et al. (12), where a higher rate of positive culture was noted from abscess aspirates. Forty-eight percent of the blood cultures were positive in their study, which is higher than noted in this study. A possible reason why abscess cultures were not positive in a fair proportion of patients is that empiric antibiotics were started on initial suspicion of the diagnosis of a PLA. Aspirates were sent when the diagnosis was confirmed and drainage was deemed necessary – based on the collection size or poor clinical response to antibiotics. Antibiotic treatment may have rendered the collections sterile when drainage was done. *Klebsiella* has emerged as the most common pathogen isolated from PLA in studies from Asia (11,14,20,28) and is associated with diabetes mellitus (30) and cryptogenic abscesses. Cerwenka (30) showed that organisms isolated in Southeast Asia differed from those isolated in central Europe. *Klebsiella pneumonia* was seen predominantly in the former (30) and has become the leading cause of pyogenic liver abscesses in South and East Asia (6,12). In Central Europe, the causative agent is more likely to be *Staphylococcus, Streptococcus* or *E. coli.* North and South American studies show a preponderance of *E. coli* (3,7,28,30) and *Streptococci* (3,28,30). In the USA, the most common organisms identified are *Streptococcal* species and *E. coli,* with 16.3% being polymicrobial (3). The predominance of gram-negative bacteria is consistent with Asian studies, which report a high prevalence of *Klebsiella* species and *E. coli* in PLA (6,18).

Management

The management of PLAs includes broad-spectrum antibiotic therapy to cover commonly isolated organisms. Antibiotics are used as standalone treatments for patients with small abscesses (≤5 cm diameter). Drainage is advised in PLAs greater than 5cm (9). Antibiotics in combination with percutaneous drainage, have become the standard of care for patients who require drainage, with surgery reserved for complications (14,28). Greater success rates are noted with percutaneous catheter drainage compared to aspiration alone (13,31) and is the favoured management option in this and other studies (17). A large proportion of amoebic liver abscesses, if uncomplicated, will respond to metronidazole alone (21). However, if the abscess is greater than 10 cm or there is a failure to respond clinically to metronidazole it should be drained percutaneously under ultrasound guidance (19,21). Other indications for drainage include left-sided abscesses and superficially located abscesses. There is a grey area for the need for intervention of amoebic abscesses between 5 cm and 10 cm in size. Bammigatti et al. (32) found no significant difference in outcomes in patients randomised to metronidazole alone or percutaneous drainage in uncomplicated amoebic abscesses greater than 5cm. The large median size of PLA and amoebic liver abscesses and the finding that 76.8% of PLA were greater than 5cm and 63.7% of amoebic abscesses were greater than 10cm, accounts for the large proportion of patients requiring image-guided percutaneous drainage in our institutions. The other reason for the high rate of percutaneous interventions is that both institutions function as tertiary referral hospitals, and many patients were transferred for percutaneous drainage from base hospitals. Failure of percutaneous drainage is associated with communication of the abscess with the biliary tree and importantly an obstructed biliary tree (14). ERCP and biliary drainage procedures were adjunctive treatment modalities required in 25% of patients with biliary obstruction and PLA and 11% of amoebic abscesses with biliary communication. Open surgical drainage has primarily been employed as a rescue modality for failed percutaneous treatments or in cases of rupture (17). Surgery was done mainly in patients who presented with ruptured liver abscesses.

World Health Organisation treatment guidelines for hydatid disease advocate for single, asymptomatic cysts less than 5 cm to be treated with albendazole alone. Surgical treatment is reserved for symptomatic cysts, cysts greater than 10 cm and complicated cysts (33). The options are a pericystectomy, open cystectomy, partial hepatectomy or lobectomy. Percutaneous options include drainage of infected cysts or the PAIR (puncture, aspiration, injection, re-aspiration) procedure. In patients with hydatid disease, 45% required surgical

intervention. Albendazole was the agent used as chemotherapy pre and post-operatively in our setting. These agents can also be used as a stand-alone treatment in cysts less than 5 cm in size or patients unfit for surgery (11). Surgery offers a high cure rate and is advised in patients with large active cysts with multiple daughter cysts or superficially located cysts with an increased risk of rupture (11). PAIR procedure is effective in solitary, active cysts greater than 5 cm (34). It is an option for patients who require drainage but are unfit for surgery or refuse surgery. It is also a management option for recurrences after surgical intervention. Eleven percent of patients underwent PAIR procedure in our institutions, which is comparable to other studies (34).

Outcomes

The mortality rate from pyogenic liver abscesses is notably high if not promptly and adequately treated. Mortality has decreased in recent years due to the effective use of broad-spectrum antibiotics and percutaneous drainage. The mortality rate was 3.0%, with no deaths occurring in the amoebic and hydatid groups. This likely does not reflect the actual rate of mortality in our setting but rather a limitation in the administrative database to capture mortality data. The mortality rate of PLA reported in the literature has a wide range (3-30%) (3). Meddings et al. (3) reported a mortality rate of 5.6%, Pang et al. (12) 6.3% and Santos-Rosa et al. (7) 20%. Uncomplicated amoebic abscesses have a mortality rate of less than 1% (21). A South African study showed a mortality rate of 0% in uncomplicated disease, which rose sharply to 25% when complications arose (21). In a study by Ghosh et al. (2), where amoebic abscesses predominated, a mortality rate of 2.5% was reported. All deaths in their study occurred in patients who had surgical intervention (2). Ruiz-Hernandez et al. (17) evaluated factors contributing to mortality in PLAs and found that older age, sepsis, higher bilirubin levels, biliary and cryptogenic origin, and the development of pneumonia were related to mortality. Only septic shock was noted to be a predictor of mortality, a finding noted in other studies too (3). This study did not find any statistically significant difference in patients who demised when age, septic markers, bilirubin levels and co-morbidities were analysed. Due to the small number of deaths, logistic regression analysis could not be done to ascertain predictors of mortality.

Limitations

This study's limitations are that the data's validity depends on the accuracy of the discharge records as it was an administrative database review rather than a review of clinical medical records. This was partially ameliorated with cross-referencing laboratory and radiology records. ICD 10 and procedure codes were used to identify patients in this study. Misclassification may have led to the underrepresentation of data. This study noted low numbers of patients with hepatic Echinococcus and did not necessarily reflect the number of patients treated in our institutions. Some patients are diagnosed and managed in the outpatient clinics and therefore were missed. This affected the ability to draw significant conclusions in this subgroup of patients. The radiology reports had missing size data in 38% of cases and scans before 2018 were not stored for images to be reviewed. This was a source of bias for radiology data interpretation. Since the data was extracted from discharge summaries, information regarding patient outcomes following discharge was not available. The in-hospital mortality data is also likely to be underrepresented as it relies on this data being updated in the discharge records. Nevertheless, the findings of this study are an important contribution to the body of knowledge regarding these pathologies in South Africa and other LMICs. Additionally, this study forms the basis for future more detailed and prospective research.

5. CONCLUSION

Liver abscesses pose a diagnostic challenge due to the non-specific clinical findings and, in the context of PLA, require prompt and accurate diagnosis due to high mortality rates. In this study, the most common presentation was PLAs in middle-aged males. HIV and diabetes mellitus were comorbidities noted in a significant proportion of patients. In PLA, biliary aetiology predominated and the organism most often cultured was *Klebsiella* species. Non-operative management via percutaneous drainage was sufficient in most cases, with surgery used to treat complications. A finding unique to this study was the high rate of HIV in all groups, which was significantly higher in the amoebic and hydatid groups. Immunosuppression in diabetic patients has been shown to affect presentation and outcomes in patients with PLA. The high burden of HIV in South Africa potentially puts these patients at higher risk of developing liver abscesses and may predispose them to worse outcomes. Whilst this did not impact outcomes in this study, further prospective studies are required to ascertain the impact of immunosuppression from HIV in these patients.

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APPENDIX A: APPROVED PROTOCOL

Clinicopathological presentation of liver abscesses at two Johannesburg Academic Institutions

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Abstract

Hepatic Abscesses represent infection of the liver parenchyma from bacteria, fungi and parasitic organisms. Trends in both the microbiology and management of liver abscesses has changed over the past decade. Currently there is a paucity of published data regarding the clinicopathological features of liver abscesses in the South African context.

This study aims to evaluate clinicopathological patterns of liver abcesses presenting at two major Wits training platforms in Johannesburg. Using data captured from hospital records, National Health Laboratory Services (NHLS) databases and PACs radiology system, the demography, presentation, microbiology, management and outcomes of patients managed at the centres will be analysed.

Literature Review

Introduction/ Background

Liver abscesses represent a suppurative infection of the hepatic parenchyma from bacteria (pyogenic), parasites and rarely fungi(1). Mixed aetiology can occur with bacterial superinfection of a parasitic abscess.

Pyogenic liver abscesses remain the most common in the developed world. Amoebic liver abscesses are notably more common in South East Asia and in Africa(1). Entamoeba histolytica (E. histolytica) and Echinococcus are usual abscess-causing liver parasites. There are definite distinctions between the microbiology, demographic characteristics and clinical behaviour noted in different geographical areas and population groups(2).
The understanding of disease factors as well as the microbiological agents associated with liver abscesses are of vital importance as it has direct implications for treatment. The next sections present a review of various types of infected liver collections; namely pyogenic, amoebic and hydatid disease

Pyogenic Liver Abscesses

A pyogenic liver abscess is a suppurative infection of the liver parenchyma. The aetiology of pyogenic liver abscesses has historically been related to bacteria entering the portal circulation via appendicitis, diverticulitis, intra-abdominal infection or biliary obstruction (1). In recent years, gallstone disease and its complications, in conjunction with other biliary tract pathology and instrumentation, have overtaken appendicitis as the leading cause of pyogenic liver abscesses (3,4). Cholangitic abscesses are a unique form of pyogenic liver abscesses occurring in relation to biliary tract pathology.

The incidence of pyogenic liver abscesses differs across population groups. In the United States, an incidence of 4.1% has been reported, whilst in Canada and Denmark incidences of between 1,1 and 2,3 per 100,000 individuals have been published (5). This is in contrast to the east where incidences are as high as 17,6 per 100,000 individuals (5,6). The maximum incidence appears to be between the ages of 50 – 70, with a male predominance (3). It has been suggested that higher incidences of PLAs are related to the aggressive management of neoplasms, increased use of biliary stents and recurrent cholangitis with resistant organisms(7,8).

Cerwenka (9) showed that organisms isolated in Southeast Asia differed from those isolated in central Europe. Klebsiella pneumonia was seen predominantly in the former (9) and has become the leading cause of pyogenic liver abscesses in South and East Asia (2,3). Klebsiella pneumonia has been linked to diabetes mellitus as well as cryptogenic abscesses (3). In Central Europe the causative agent is more likely to be Staphylococcus, Streptococcus or Escherichia coli (E. coli). A separate study in Europe reported 53.5% positive microbiology, either on blood culture or pus aspirate, and correlate with the findings of Cerwenka showing a predominance of E. coli and Streptococci (10). In the USA, the most common organisms identified are Streptococcal species and E. coli, with 16.3% being poly microbial (5).

Pyogenic liver abscesses usually present with abdominal pain, fever, and anorexia (4,7) and less commonly nausea, vomiting, and weight loss. A small proportion of patients may present with cough or dyspnoea when the liver abscess is associated with a pleural effusion (7). Examination often reveals a tender hepatomegaly with exaggerated tenderness with percussion over the lower ribs (11). Jaundice appears to be less common and occurs in the later stage (4,11). Occasionally a patient may present without right upper quadrant pain and jaundice, but with pyrexia of unknown origin (11).

Commonly associated co-morbidities include diabetes mellitus and pancreaticobiliary malignancy (8). Notably patients from Europe are older with biliary abnormalities or malignancy; whereas those from Southeast Asia are diabetic and the cause of infection was cryptogenic (9). Diabetes mellitus has been noted in multiple studies to present in patients with pyogenic liver abscesses and thus suggests that the hosts immunity is implicated in the pathogenesis(8,12). Not many studies exist considering HIV as a co morbid factor, but HIV reactivity has been reported to be around 2% (4).

Laboratory abnormalities include elevated white cell count, C- reactive protein and procalcitonin (3,13). Hyperbilirubinemia is uncommon, and if present is usually mild(3). Other derangements in liver function testing includes raised alanine transaminase (3,12) and hypo-albuminaemia. Some studies have shown association between alkaline phosphatase and the volume of the abscess, the larger the abscess the higher the alkaline phosphatase (4).

Abdominal ultrasound, the diagnostic modality of choice, has sensitivities ranging from 92-97% (4,7). Right lobe liver abscesses are the predominant finding due to the streaming effect

of the portal circulation. Segments 6 and 7 of the liver are more commonly involved. The right lobe of the liver receives blood from the right colon. The primary site for intestinal amoebiasis is the right colon and many conditions predisposing to formation of pyogenic liver abscesses occur on the right side of the colon(4). Pyogenic abscesses tend to present as multiple abscesses on imaging. Ultrasound can also be used to delineate abnormalities with the biliary tract that may predispose to abscess formation.

The management of patients with pyogenic liver abscesses currently entails:

1. Resuscitation and stabilization with intravenous fluid infusions and analgesia.
2. Broad spectrum antibiotics
3. Specific treatment of the abscess (either operative or non-operative strategies)

With reference to antibiotics, third or fourth generation cephalosporins in addition to metronidazole or carbapenems are the initial agents of choice (3), however, piperacillin-tazobactam and amoxicillin clavulanic acid can also be used (1). Antibiotics can be tailored according to the culture once an organism and sensitivity has been identified (3).

Regarding specific therapeutic interventions small liver abscesses with sizes less than 3- 5cm can be treated with antibiotics alone (1). Various studies have reported 80-100% success rates when treating abscesses less than 5cm with only antibiotics (1). Whilst no clear guidelines exist for the duration of antibiotic therapy, most authors advocate 2 to 6 weeks of therapy (1,3,12) . The current trend in management has moved to minimally invasive drainage techniques in abscesses greater than 5cm. Percutaneous drainage, either commuted tomography scan (CT) guided or ultrasound guided, has now become the most common approach (3,14). In patients who had abscesses larger than 5cm percutaneous drainage via a pigtail catheter is used (4). In institutions where percutaneous drainage is the first line treatment, the need for surgical drainage drops to as low as 4%. The indications for surgical drainage are rupture of the abscess, sites inaccessible to percutaneous intervention and failure of response to conservative therapy. Mortality was increased in the groups of patients receiving surgical drainage, however this may represent bias as surgery in this context was not used as the first line treatment modality but rather as a rescue (4). Some authors suggest that surgery can be as effective as percutaneous drainage if used as a first line treatment for abscesses greater than 5 cm(4).

While the mortality rate of liver abscesses has decreased over the past decade, outcomes vary in relation to patient co-morbidities. A reported 11% of patients presenting with pyogenic liver abscesses may develop septic shock and require intensive care (3). In these patients, diabetes mellitus was associated with septic shock as well as longer duration of hospital stay (3). Complications associated with pyogenic liver abscesses can be as high as 60% and include pulmonary complications (7); pleural effusions, consolidation and empyema. Portal vein thrombosis and super mesenteric vein thrombosis may also occur. The liver abscess may rupture into the abdominal cavity causing peritonitis, or rupture into the biliary tract and gastrointestinal tract. Higher rates of complications and morbidity were noted with the presence of higher bilirubin and creatine levels(7).

Hepatic abscesses are associated with high mortality if not promptly and adequately treated. The rates of in hospital mortality range from 3-30% (5,10). A population based study of liver abscesses in the United States conducted between 1994-2005 reported a mortality rate of 5,6% (5) whilst a European study reported a mortality rate of 10,6% A more recent retrospective study in East china reported a mortality rate of 0,9% (3). Significant risk factors associated with mortality were ages between of 65-85 (7). A higher mortality rate was also noted in patients with 3 or more co-morbidities (3). This is specifically related to patients with chronic renal failure, cirrhosis and malignancy. Diabetes mellitus, pre-existing biliary disease or chronic liver disease is not associated with increased mortality (5,7). Septicaemia and malignancy are also noted to be strong indicators of mortality (10).

Amoebic Liver Abscesses

About 10% of the world's population is infected with Entamoeba histolytica (11). The distribution of disease varies, however, it is often seen in developing countries (4) and is more prevalent in tropical and subtropical climates (11). Studies in India have shown a higher incidence of amoebic liver abscesses, with up to two thirds of cases being due to amoebiasis (4). The patient profile generally was younger patients (mean age 41 years), with a male predominance and a high alcohol intake (4,15). Few local studies exist reporting the prevalence in a South African setting (a pity as amoebic liver abscess is a common clinical problem in most South African hospitals). However, the prevalence has been reported to be around 0.5% (16). The amoebic parasite is transmitted via the faeco-oral route and thus is seen in low socio-economic groups (11,15). The two most common symptoms are right hypochondrial pain and fever (15); patients may appear toxic and chronically ill looking (11). The incidence of

diarrhoea as a presenting symptom ranges from 12 to 33% (17). Jaundice and ascites may be noted and is seen in patients with multilocular abscesses (17).

Serological tests for amoebiasis are a rapid and reliable way of diagnosing extra-intestinal amoebiasis (17), however, these tests may be misleading in endemic areas as a result of previous infection(11). Other laboratory investigations often reveal a leucocytosis, with a predominance of polymorphonucleocytes, raised erythrocyte sedimentation rate and anaemia (11,17). As with pyogenic disease, raised alkaline phosphatase and hyperbilirubinemia is seen only in severe disease (11). Ultrasonographic features demonstrates a solitary, well defined cystic, intrahepatic cavity; most commonly found in the posterior part of the right lobe (4,11). The aspirate from the abscess is typically referred to as 'anchovy paste' in colour and is due to liquefactive necrosis of the liver (10).

A large proportion of amoebic liver abscesses, if uncomplicated, will respond to metronidazole alone. However, if the abscess is greater than 10cm it should be drained percutaneously under ultrasound guidance (11). Other indications for drainage are: failure of antibiotic therapy alone after 48-72 hours, large left sided abscesses where a pyogenic abscesses cannot be ruled out, or if there is impending pleural or peritoneal rupture (16). Surgical treatment is indicated for rupture causing amoebic peritonitis.
Pleuropulmonary complications noted most frequently are pleural effusions and atelectasis (17). Rupture of amoebic abscess can occur intraperitoneally, resulting in amoebic peritonitis, or intrathoracically (pleural or pericardial collections) (11). Complete resolution of the abscess cavity can take up to 6 months (17). Alcoholism is related to the presence of larger abscesses, delayed resolution and a higher complication rate (17). Uncomplicated abscesses have a mortality rate of less than 1 percent if treatment is started early. Mortality has been reported to be as high as 17 percent with risk factors being high bilirubin level, low albumin or large abscesses(19).

Hydatid Liver Collections

Hydatid disease is a public health problem in South America, the Middle East, Western China and some sub-Saharan African countries. It is caused by the tape worm Echinococcus (11). Human infection can be caused by 4 species – E. granulosis and E multilocularis most commonly and rarely E Vogeli and E. Oligarthrus. Canines are the definitive hosts whilst

humans are the intermediate host. Infection can result in cysts forming in any part of the body, but 60 percent occur in the liver and 25 percent in the lungs (11).

Primary infection is usually asymptomatic, with latency periods of up to 50 years. Hydatid cysts that are small or calcified may be asymptomatic indefinitely (20) and symptoms are uncommon before the size of the liver cyst is greater than 10 cm. Patients may present with hepatomegaly and right upper quadrant pain. Pain is attributed to pressure from the cyst (11). Symptoms may also be due to complications such as secondary bacterial infection or rupture. Rupture into the peritoneal cavity can result in peritonitis, severe anaphylactic reactions or seeding to other viscera (11); rupture into the biliary tree causes obstructive jaundice and cholangitis.

Serology is used for primary diagnosis and follow up and includes complement fixation and indirect hemagglutination (10). E. granulosa infection produces leucopaenia, thrombocytopaenia, mild eosinophilia. Ultrasound is used most widely as it is easy to perform, inexpensive and it has a sensitivity of 95 percent (22); CT scan may be used if greater detail is needed to ascertain the location and presence of daughter cysts. Ultrasound features are a round, smooth, anechoic cyst. Daughter cysts may produce characteristic internal septation. Inactive lesions are typically collapsing or flattened cysts, with coarse echoes and cyst wall calcification.

WHO guidelines advocate for single, asymptomatic cysts less than 5cm be treated with albendazole alone (20,22). Surgery is the management of choice for all symptomatic cysts, cysts greater than 10cm, complicated cysts and cysts with multiple daughter vesicles (11,23). Both conservative and radical approaches have been described. The preferred surgical method is removal of an intact cyst, if possible. Alternatively, the cyst is aspirated or opened, sterilised with a scolicidal agent and then excised. In both cases the cavity is filled with omentum (11,20). The radical approach includes partial hepatectomy and total pericystectomy (24). Albendazole is used 1 week prior to surgery and four weeks post-surgery to minimize secondary echinococcus that may be caused by fluid spillage into the abdominal cavity. In recent years, the minimally invasive percutaneous procedure PAIR (puncture, aspiration, injection, re-aspiration) has been used for cysts more than 5cm in size without daughter cysts (23). Hydatid disease can relapse years after appropriate treatment and thus a 5 year follow up is recommended. The mortality rate reported in the literature is 0 to 6,5 percent (24).

Rationale for the study

From the literature discussed above, it is evident that the epidemiology and the aetiology of liver abscesses has changed over the past few decades. The aetiology and characteristics of liver abscesses has a direct impact on management. Patient co-morbidities has been shown to influence outcomes. Most of the published literature comes from the United states of America and Asia (Japan, Taiwan, Korea) (26). Currently there is a paucity of published data to evaluate these parameters in a South African and African context. The Hepatobiliary units at Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) serve a wide referral area, and are thus ideal to evaluate the main aim of this study.

South Africa has a high burden of HIV and AIDs and not many studies have looked at whether this has an impact on presentation and outcome of liver abscesses. This study will look at HIV positivity and what implications it has for patients with liver abscesses treated at the study sites.

Understanding the epidemiology, aetiology and microbiology of liver abscesses will then serve as a guide to tailor management practices better. In addition, this study will serve as a reference for further studies regarding liver abscesses in South Africa.

Study Aim

Aim:

Analysis of the clinicopathological patterns of liver abscesses at two Witwatersrand training hospitals in Johannesburg.

Primary Objectives:

To describe the demography, clinical, radiological and laboratory presentations of infective liver collections at the selected centres.

Secondary objectives

To describe various management modalities

Analyse outcomes in terms of morbidity, mortality, intensive care and/or high care stay as well as total length of hospital stay

To analyse the impact of non-HIV co-morbidities on patients' presentation and outcome

To describe the impact of HIV comorbidity on presentation and outcome

Assess differences in patients with complicated versus uncomplicated disease

Methods

Design

A descriptive study analysing retrospective data on liver abscesses presenting to the study sites from January 2012- December 2018

Site of Study

The Hepatobiliary units at CHBAH and CMJAH

Study population

All adult patients (13 years and older) presenting with liver abscesses

Sampling

Patients will be sourced via the electronic discharge summary data base and then further information retrieved from the hospital records, NHLS data base and the PACs radiology system.

Inclusion Criteria

All patients aged 13 years and above managed for infective liver (hepatic) collections at the study centres from January 2016 – December 2020.

Data Collection

Data sheets will be used to record data for each patient in RedCap. This will be exported onto Excel for analysis. Appendix A shows example of data sheet.

Sources of bias

Although this a review of data collected from standardized databases, the retrospective nature and possibility of incomplete information may potentially skew the analysis. In addition, the units are referral centres, thus the data may not reflect the general population. Despite this, the study will still serve as important reference for further studies on liver abscesses.

Data Analysis

Data analysis will be performed with the Wits approved Statistical software. Descriptive statistics will be used for continuous variables, and will be expressed as the mean (with standard deviations) or median and ranges. Categorical variables will be expressed as percentages. Differences between groups will be evaluated by Mann-Whitney test and one way ANOVA, with p values of <0.05 considered as statistically significant.

Ethics

Clearance to proceed with the above study will be obtained University of Witwatersrand Human Research Ethic Committee

Timing

	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Literature review	X	X											
Preparing protocol			X	X	X								
Protocol assessment						X	X						
Ethics application								X	X				
Collecting data										X	X		
Data analysis											X	X	
Writing up - paper													X

Funding

No major costs are anticipated and thus funding will not be required. Minor costs of photocopying, printing and travel will be covered by the candidate.

Problems

As this project is a retrospective study the major problem would be incomplete records and missing records.

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APPENDIX B: DATASHEET

Patient	1	2	3	4	5
Age					
Gender					
Presenting complaint					
Fever					
RUQ pain					
Nausea/Vomiting					
Jaundice					
Loss of weight					
Risk Factors					
Diabetes					
Cirrhosis					
Malignancy					
CRF					
HIV					
Biliary disease					
Other					
Laboratory findings					
WCC					
CRP					
PLT					
HB					
ALT					
AST					
GGT					
ALP					
Bilirubin					
Urea					
Creatinine					
INR					
Hydatid Serology					
Amoebic Serology					

Radiology					
U/S					
CT					
MRI					
Size					
Microbiology					
Blood Culture					
Abscess Culture					
Polymicrobial					
E. Coli					
Streptococci					
Anaerobes					
Enterococcus					
Staphylococci					
Amoebic					
Hydatid					
Management					
Antibiotics only					
Antibiotic duration					
Percutaneous drainage					
Pigtail					
Aspiration					
ERCP					
Surgery					
Clinical Outcomes					
ICU					
High Care					
Complications					
Length of hospital stay					
Mortality					

APPENDIX C: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2021/06/30

Dr K Pillay
School of Clinical Medicine
Department of Surgery
Medical School
University

Sent by e-mail to: krevoshap@gmail.com

Dear Dr Pillay

Re: **Protocol Ref No:** M200245
Protocol Title: *Clinicopathological presentation of liver abscesses at two Johannesburg academic institutions*
Principal Investigator: Dr K Pillay

Thank you for your letter of 2021/06/22.

I confirm that we have noted and approve of your proposal to move your data collection window to the period 2016/01/01 to 2020/12/31.

I further note that you have satisfied the two conditions on your original ethics Clearance Certificate and have therefore attached an updated Certificate to this letter.

Thank you for keeping us informed.

Yours Sincerely

I. Burns
.....
Mr I Burns
For the Human Research Ethics Committee (Medical)

CB Penny
.....
Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr K Pillay

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200245

NAME: (Principal Investigator)	Dr K Pillay
DEPARTMENT:	School of Clinical Medicine Department of Surgery Medical School University
PROJECT TITLE:	*Clinicopathological presentation of liver abscesses at two Johannesburg academic institutions*
DATE CONSIDERED:	2020/02/28
DECISION:	Approved unconditionally
CONDITIONS:	Previous conditions satisfied on 2021/06/30
SUPERVISOR:	Dr JAO Omoshoro-Jones
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/07/09

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **February** and therefore reports and re-certification will be due in the month of **February** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

APPENDIX D: TURN IT IN REPORT

Draft 4.docx

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