A RETROSPECTIVE RECORD REVIEW OF CHRONIC HEPATITIS B PATIENTS ATTENDING A QUARTENARY JOHANNESBURG HOSPITAL

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A RESEARCH REPORT

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Declaration

I, Nsekela Leticia Mfuta, do hereby declare that this research report is my unaided work. It is being submitted for the degree of Master of Medicine (MMed) in the branch of Internal Medicine. This research report is submitted in the submissible format (with my protocol and extended literature review) as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other University.

Signed _____  _____ on the

21st day of November 2024 in Johannesburg

Dedication

"When you pass through the waters, I will be with you; And through the rivers, they shall not overflow you. When you walk through the fire, you shall not be burned; Nor shall the flame scorch you.”- Isaiah 43:2 NKJV Holy Bible

This work is dedicated to my beloved parents. Firstly, the loving memory of my late father Dr Tshibemba Gaston Mfuta, your memory and legacy endure in all our lives forever. You remain ethereal in my mind. A secondly, my brave mother Mrs Nsekela Madeleine Mukendi Mfuta, you remain a defiant force and I am humbled to be raised and loved by you. Twasakidila wa bungi.

Acknowledgements

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Abbreviations

AFP	Alpha feta protein
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core antibody
APRI	AST to Platelet Ratio Index
cccDNA	Covalently closed circular DNA
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ETV	Entecavir
GI	Gastrointestinal
HBcRag	Hepatitis B core-related antigen
HBeAg	Hepatitis B e Antigen
HBRN	Hepatitis B Research Network
HbSAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
IFN- α	Interferon A
KZN	KwaZulu Natal
LDL	Lower than detectable
MASLD	Metabolic associated steatotic liver disease
mRNA	Messenger RNA
NA	Nucleotide Analogues
NUC	Nucleotide/side analogues
P22Cr	22-kDa precure protein
PLWHIV	People Living With HIV
SA	South Africa
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
ULN	Upper limit of normal
u/l	Units per litre
WHO	World Health organisation

Chapter One

Protocol with extended literature review

1.0 Introduction

Chronic infection with the hepatitis B virus (HBV) affects approximately 316 million persons across all ages worldwide (1) and was responsible for 887 000 estimated liver-related deaths globally in the year 2015 (2). These statistics make it the most common chronic viral infection worldwide (3), with significant morbidity and mortality in endemic areas such as Sub Saharan Africa. Despite advancements in primary prevention as well as treatment of the disease, it still poses a significant burden to the public health landscape of Sub-Saharan Africa and very little research has been done into its natural history in this region.

1.1 Pathogenesis

Hepatitis B is a member of the hepnaviridae family of viruses. These are small viruses which have partially double stranded DNA. Upon acute exposure, the HBV enters hepatocytes and encodes itself in the nucleus. Within the nucleus of the cell, the partially double stranded DNA is repaired resulting in the formation of the covalently closed circular DNA (cccDNA). This acts as the transcriptional template for viral messenger RNAs (mRNAs). The RNA genome which has been formed together with reverse transcriptase allow for reverse transcription within the cytoplasm. Cytoplasmic viral capsids which contain mature viral DNA, thereafter, travel to the nucleus to replenish the cccDNA or bind to HBV surface antigens which have formed on the endoplasmic reticulum. Through this process, virions are secreted through the cellular membrane. Due to its dynamic pathogenicity, although an individual can clear hepatitis B surface antigen (HBsAg), the hepatocyte carries HBV DNA in the form of cccDNA which remains incorporated in the cell nucleus (4).

It has various methods of transmission including perinatal, blood borne, sexual, as well as horizontal transmission via close person-to-person contact, especially in high endemic areas. This makes hepatitis B up to 100 times more transmissible than HIV (4).

1.2 Epidemiology

An estimated 2 billion people worldwide show evidence of past or present HBV infection (2). The mortality due to chronic HBV is increasing, with a reported 500 000 – 1.2 million deaths occurring per year. In contrast, mortality due to HIV/AIDS is on the decline largely due to better screening and the use of antiretrovirals. Despite the distribution of multiple societal guidelines, poor access and limited resources have resulted in an inadequate detection of chronic HBV in Sub Saharan Africa. It is estimated that 95% of chronic HBV carriers are unaware of their status (5).

Over two thirds of the global burden of HBV is found in the Western Pacific and African regions (5). There is a higher prevalence of chronic HBV in lower socio-economic countries such as those in Sub Saharan Africa, where the prevalence is estimated at 4.6-8.5%, compared to rates of 0.4-1.6% in the United States (2). A study into the seroprevalence of hepatitis B in KwaZulu Natal (KZN) conducted between June 2014 and June 2015, estimated that 3.5 million persons in South Africa (SA) are infected with virus (6). Data shows that there are higher seroprevalence rates among men in comparison to women, as well as in rural areas compared to urban areas (5).

Fortunately however, the burden of chronic HBV has been limited due to the introduction of effective vaccination programmes (2). The HBV vaccine is offered in 47 of the member states of the World Health Organization (WHO). The three dose vaccine coverage in these areas is

estimated to be 77% (7). There has been a significant decline in chronic HBV prevalence over time because of vaccination programmes mostly targeted at children below the age of 5 years. Implementing vaccination during childhood is essential as an estimated 30 – 50% of children infected below the age of 5 years, go on to develop chronic HBV as adults (1). Countries such as China, which was a previously high endemic area, has carried out catch up vaccination programmes and increased surveillance since 1992, which has resulted in it becoming an intermediate endemic area (8). Despite the introduction of birth dose vaccination in some countries in Sub Saharan Africa, coverage in this region has been low, peaking at just 11% (7).

In SA, the vaccine was introduced into the expanded programme of immunization in 1995 and in 2015 the hexavalent vaccine was implemented in preference to the pentavalent vaccine. Prior to immunisation, an estimated 6.5 million South Africans were HBV carriers, with the most affected population groups being school-aged children, people living in rural areas and sexually active people. In the same study looking at the seroprevalence of hepatitis B, it was found that the age group with the highest prevalence were the 15–49-year-olds (prevalence of 4%). Prevalence of chronic HBV amongst 15-19 year olds still remain high, with a seroprevalence of 1.1% in males and 0.9% in females, inferring failed immunization strategies (6). Despite WHO recommendation to introduce the birth dose vaccination, SA has not as yet provided an implementation plan and remains undecided. In contrast, in China implementation of the birth dose vaccine as well as updating their vaccine strategy with catch up programmes has reduced the HBsAg seroprevalence from 9.67% in 1992 to 0.96% in 2009 (5).

In 2016, the WHO proposed a framework to end all forms of viral hepatitis by 2030. The goals in this framework include the following impact targets to be achieved by 2020:

- A reduction by 30% of new cases of chronic HBV as well as hepatitis C virus (HCV).
- A reduction by 10% of HBV and HCV related deaths (7)

As of 2019, 68 of the 194 member states of the WHO had achieved the 2030 target of all age HBV-related death rate of 4 per 100 000. As of 2019, there was a 30% reduction in new cases of HBV and a 10% reduction in HBV related deaths in 2019 . Despite these valiant efforts, the Western Pacific and African regions remain the most endemic with prevalence rates of 7.1% and 6.5% respectively. Chronic HBV is still the leading cause of death from liver cancer and the third largest contributor to liver cirrhosis, responsible for 331 000 global deaths. Due to population growth and ageing, the number of chronic HBV related deaths are growing, which calls for better implementation of key interventions such as cost effective antiviral treatment, and development of functional cures for chronic HBV (1).

1.3 Natural History

Despite advances in the prevention and treatment of chronic HBV infection, data on chronic HBV in Sub Saharan Africa and particularly in South Africa, remains sparse (3). There is limited data on the natural history of chronic HBV in SA and associated risk factors for disease progression within this region.

HBV is not pathogenic on its own and the presence of disease is an interplay between viral replication and the host immune response (9). Post primary infection, the clinical course of disease is varied (10). Chronic HBV infection is defined as the persistence of hepatitis B surface antigen (Hep B S-Ag) for more than six months post primary infection (2). The rate of progression from acute to chronic HBV is largely determined by the age of onset at primary infection (10). In perinatal cases of transmission, 98% of new-borns become chronic HBV carriers (11). In contrast, amongst adults who are acutely infected, up to 3-5% develop chronic HBV (12).

Historically, chronic HBV infection was divided into 5 phases, taking into consideration the level of infectivity inferred by HBeAg positivity, the level of immune activity perceived as fluctuations in alanine aminotransferase (ALT) and HBV DNA copy levels (4). The clinically defined phases shown below (Table 1).

Table 1.1: South African guideline for the management of chronic hepatitis B (4).

Stage	**Serological Characteristics**	**Clinical Progression**
Immune Tolerant	HBeAg positive High levels of HBV DNA (>2000 copies) Normal ALT	Minimal signs of fibrosis Slow progression to cirrhosis
Immune clearance	HBeAg positive Lower levels of HBV DNA Elevated ALT	Histologically more severe necroinflammation May last several weeks to years and may lead to HBeAg seroconversion (development of anti-HbE) More rapid progression to cirrhosis
Inactive carrier/latent	Anti-HBe antibodies Low/undetectable HBV DNA Normal ALT	Good prognosis Low risk of progression to HCC/cirrhosis Spontaneous anti-Hbs antibodies may occur
HbeAg negative	HbeAg negative Fluctuating ALT and HBV DNA levels Low levels of anti HBc IgM may be found	More common in older men Significant levels of necroinflammation and progressive fibrosis
Occult HBV	HBSAg negative Low levels of HBV DNA HBeAg negative	No liver disease but risk of reactivation with immune suppression

The South African guidelines for the management of chronic HBV last published in 2013, still refers to this classification of clinical phases. It's important to note that these clinical phases are not linear. By contrast, the European Association for the Study of the Liver (EASL) 2017 clinical practice guidelines on the management of HBV classifies chronic HBV based on the (a) infectivity, i.e., HBeAg positivity and (b) the presence or absence of liver disease (13). This classification provides a clearer impression of when treatment should be initiated.

Table 1.2 **:** EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. (13)

	HBeAg Positive		**HBeAg Negative**	
	Chronic Infection	**Chronic Hepatitis**	**Chronic Infection**	**Chronic Hepatitis**
HBSAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2000 IU/ml	>2000 IU/ml
ALT	Normal	Elevated	Normal	Elevated
Liver Disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune clearance	Inactive carrier	HBeAg Neg

The Hepatitis B Research Network (HBRN), a network of investigators based in the United States (US) and Canada, have created a database of chronic HBV carriers across 21 clinical centres in North America, and it provides valuable data on the clinical characteristics of chronic HBV. In a study conducted on treatment naïve patients to determine their clinical characteristics and risk factors for disease progression, 78% of the 1625 patients were HBeAg negative at baseline, with 13% not meeting any clinical criteria for any prescribed clinical phase. Within this study cohort, 43% had low level increases in their ALT (1-2 x the upper limit of normal) (14).

1.4 Extrahepatic Manifestations

The spectrum of chronic HBV is not limited to hepatic disease, with patients also being at risk of extrahepatic manifestations. Postulated mechanisms for extrahepatic disease include the circulation of immune complexes; the presence of circulating viral antigens; formation of local complexes by viral antigens; interactions between tissue antigens and circulating auto-antibodies and direct viral interaction with extrahepatic organs (15). Extrahepatic manifestations may be classified by organ systems as illustrated in Table 3.

The most commonly occurring extrahepatic disease in Sub Saharan Africa is glomerulonephritis. Glomerulonephritis (GN) usually occurs in children and is more common in males. It typically presents as nephrotic syndrome and usually runs a self-limiting course without significant renal disease. However, in adults the disease can slowly progress to renal failure. Viral antigens which have been identified on renal biopsy include HBeAg, HBsAg and HB core antigen. Despite this, correlations cannot be made between HBV serology and renal disease as studies have shown conflicting results such as remission in proteinuria but persistence of HBeAg, whilst some studies have shown persistence in proteinuria despite HBeAg seroconversion (15).

Table 1.2**:** Extrahepatic Manifestations of Chronic HBV (15).

	Extrahepatic Manifestation
Renal	Membranous GN Mesangial Proliferative GN Membranoproliferative GN
Haematological	Aplastic Anaemia Polyarteritis Nodosa Serum Sickness Essential Mixed Cryoglobulinaemia
Dermatological	Palpable purpura
Musculoskeletal	Arthritis/Athralgia

1.5 Complications

Hepatocellular carcinoma (HCC) and cirrhosis are two well recognized complications of chronic HBV. If the two were combined, chronic HBV would rank in the top 10 causes of global mortality, ranking above malaria and tuberculosis (16). In endemic areas, 12-20% of chronic hepatitis patients develop cirrhosis. Many cases of treated cirrhotic patients remain compensated, but between 20 – 23% develop hepatic decompensation and 6-15% develop HCC (10).

The combined risk of developing cirrhosis, liver failure or hepatocellular carcinoma (HCC) is 15-40%, whilst the risk of dying due to HBV related liver diseases is 15-25%. HBV accounts for 87890 deaths per annum in Sub Saharan Africa. However, data on the incidence of cirrhosis is limited as liver biopsies are not routinely done and non-invasive methods such as transient elastography are not easily accessible. Data has shown that there is a high incidence of HCC in Sub Saharan Africa, where 80% of cases are attributable to chronic HBV. This data may still be underreported due to the lack of cancer registries. The prognosis of patients with HCC is still poor with a 92% one year mortality rate in some under resourced countries (5).

1.5.1 Hepatocellular carcinoma (HCC)

As illustrated by the clinical phases of chronic HBV infection, seropositivity of HBeAg is a marker of active viral proliferation and infectivity. Literature on the prevalence of HbeAg has shown conflicting results in HCC patients, with a case series showing a lower prevalence of HBeAg in HCC patients when compared with case control studies that showed a high HBeAg prevalence in HCC. The risk of HCC however, is elevated in patients who are seropositive for both HBeAg and HB-SAg (17).

1.5.2 Cirrhosis

The diagnosis of cirrhosis is definitively made on biopsy, however access to biopsy may be limited due to resource limitations and already advanced disease (4). The diagnosis can additionally be made through non-invasive methods such transient elastography, where the stiffness of the liver can be measured. Transient elastography has been shown to have a good specificity with regards to advanced disease and fibrosis. Alternative non-invasive methods include serum biomarkers of liver synthetic function and ultrasonography (13). It is well documented that the cumulative risk for the development of cirrhosis depends on the HBV DNA level (18). However one of the limitations in Sub Saharan Africa is access to HBV DNA testing, and so the WHO has proposed guidelines to assess risk in order to determine the need for treatment (19).

1.6 Risk factors for Progression

Virological factors influencing clinical progression include:

- The presence of HBeAg, which is associated with active viral replication, prolonged replication phases and prolonged periods of necrosis and inflammation in the liver
- The presence of HBV DNA, as higher levels indicate viral activity
- HB S-Ag positivity (10)
- HBV genotype, where genotype A is prevalent in Africa and associated with progression to chronic infection, although all genotypes may progress to chronicity (11)
- Genotype A is the most prevalent in SA and has a higher rate of seroconversion with lower viral loads (19)

Non virological factors include:

- Gender, with males more predisposed to chronic infection than females

- Alcohol consumption which accelerates liver injury and risk of cirrhosis
- Obesity and metabolic associated fatty liver disease (MASLD), previously known as NAFLD
- Co-infection with hepatitis C or D, as this shortens the duration of antigenemia and lowers the peak ALT concentration (10)

1.6.1 Chronic HBV and HIV co-infection

Of the 40 million estimated people living with HIV (PLWHIV) worldwide, about 10% are co-infected with chronic HBV. Data from Africa has shown that the natural course of chronic HBV infection is altered in the presence of HIV infection; with higher levels of HBV viraemia; more frequent episodes of relapse/reactivation and a more rapid progression to liver fibrosis and HCC. Unfortunately, there is a paucity of data regarding the persistence or clearance of HBV in the presence of HIV within our context. In a study conducted on PLWHIV receiving care in KZN, it was found that at baseline, 103 persons of 4292 (2.4%) were chronic HBV carriers and that 47 of the 103 (45.6%) persons remained seropositive. Risk factors for persistence in this group included low CD4 counts (<50) and a low body mass index (3).

1.6.2 Chronic HBV and Metabolic Syndrome

The metabolic syndrome which comprises type 2 diabetes, hypertension, central obesity and dyslipidaemia is associated with non-alcoholic steatohepatitis and progressive fibrosis. The pathogenesis for fibrogenesis is linked to the secretion of adipokines such as leptin, adiponectin and resistin from the visceral adipose tissue. In chronic hepatitis C infection, the presence of metabolic syndrome has been shown to lead to a more rapid progression to cirrhosis, higher viral loads and a poorer response to treatment. There are few studies exploring the relationship between chronic HBV and the metabolic syndrome. One cohort study performed in Hong Kong

did show a direct correlation between metabolic syndrome and progression to cirrhosis in chronic HBV. Of the 1466 patients included in the study, 13% had metabolic syndrome. Amongst the patients with metabolic syndrome, 24% exhibited definitive fibrosis on biopsy, whilst 46% had signs of bridging fibrosis. Fibrosis was more frequently associated with hypertension and type 2 diabetes and more severe in patients with features of metabolic syndrome. The early recognition and management of the metabolic syndrome may reduce the risk of progression to fibrosis in chronic HBV patients (20).

1.7 Treatment

Prior to the nucleotide/nucleoside era, the lifetime risk of death in chronic HBV in China was 40-50% in males, and 15 % in females, with delayed HBeAg clearance or reactivation being a major determinant of prognosis. Fortunately, due to treatment, this has markedly improved (10).

1.7.1 Indications for Treatment

Patients eligible for treatment as per the last published SA guidelines include all patients presenting with acute liver failure, decompensated cirrhosis and those on immunosuppression (this includes patients on chemotherapy and rituximab). Chronic HBV carriers regardless of HBeAg seropositivity are treated based on their ALT levels, HBV DNA levels and non-virological risk factors for disease progression (4). In some parts of Sub-Saharan Africa, access to HBV DNA level testing is limited and whilst alternative testing models are being explored, clinicians can use the WHO guidelines to decide who warrants treatment. The WHO guidelines look at ALT levels, APRI scores and clinical evidence of cirrhosis, thereby picking up more advanced disease (19). A shortcoming of these guidelines is that they aim to treat patients with advanced disease parameters. In contrast, the literature has shown that even chronic HBV carriers with low serological activity markers and patients with clinically asymptomatic disease

can progress to cirrhosis and HCC. To overcome this shortfall, the EASL guidelines recommend treating those meeting the following criteria:

- HBeAg positive or negative with chronic hepatitis (HBV DNA >2000 IU/ml and ALT > upper limit of normal (ULN) (plus biopsy showing moderate necroinflammatory changes)
- Compensated or decompensated cirrhosis
- HBV DNA levels >20000 IU/ml and ALT 2x ULN regardless of features of fibrosis
- HBeAg positive chronic infection with normal ALT and high HBV DNA if older than 30 years
- Chronic HBV infection regardless of HBeAg seropositivity if there is a family history of HCC, cirrhosis, or extrahepatic manifestations (13)

1.7.2 Therapy Options

The two main treatment options are the use of nucleotide analogues (NA) and pegylated interferon alpha. Nucleotide analogues are preferred for their long-term antiviral efficacy leading to sustained viral suppression. They also have a favourable side effect profile, and it can be used to treat patients with decompensated cirrhosis, those on immunosuppression and patients with extrahepatic manifestations. Interferon alpha is now in limited use as it has an unfavourable side effect profile and a variable response in treatment. High barrier resistance NA's such as tenofovir disoproxil fumarate (TDF), entecavir (ETV) and tenofovir alafenamide (TAF) are preferred (13).

With the use of antivirals, there has been a low incidence of adverse clinical outcomes, including hepatic decompensation, incident cirrhosis and HCC, with a peak incidence of 2% by 7 years of treatment (21). Whilst both the use of IFN and NUC suppresses viral replication,

neither are able to eradicate chronic HBV (22). IFN is given for a limited duration, whereas NUCs can be used for many years, and often for life.

TDF and ETV have been proven to have similar efficacies, and that the more pertinent determining factor is the patients HbeAg positivity and level of HBV viraemia at baseline. The potency of antivirals (both TDF and ETV) was higher in HbeAg negative patients with a rate of viral suppression of 91-95% compared to 70-80% in HbeAg positive (23). These findings support the well understood notion that chronic HBV is an interplay between virus and host factors.

1.7.3 Treatment Endpoints

Treatment goals is to ultimately improve quality of life and prevent disease progression to known complications such as HCC and cirrhosis. This is achieved by aiming for suppression of HBV DNA levels, HBeAg loss (with or without seroconversion to anti-HBe) and normal ALT levels (13). During the course of treatment, patient's ALT and HBV DNA levels are monitored and surveillance for HCC is encouraged with monitoring of alpha fetoprotein (AFP) and routine imaging (4). Functional cure for chronic HBV is defined as sustained loss of HBsAg with or without seroconversion (13).

Whilst the use of antivirals has lowered the incidence of adverse outcomes, seroconversion and functional cure remains elusive. Studies into other serological and virological parameters and their role in determining seroconversion and their use as surrogate markers for fibrosis have begun.

1.7.3.1 Association between ALT flares and HbeAg Seroconversion

ALT levels are routinely monitored in chronic HBV patients. Rises in baseline ALT may be a serological marker of a vigorous immune response. Various definitions of flares exist, but unfortunately no universal level is defined, and the level depends on the regional guidelines. In a study conducted by the HBRN in North America in treatment naïve patients, ALT flares were associated with the reduction and clearance of viral proteins, particularly HbeAg and HBV DNA. Both patient and virus factors are associated with ALT flares, these include male sex, higher baseline HBV DNA levels, alcohol use and surprisingly older age is protective. Although ALT flares are associated with reduction of HbeAg and HBV DNA suppression, it did not lead to HBsAg loss (24).

1.7.3.2 Hepatitis B Core Antibody titre as a predictor for seroconversion

As chronic HBV is a disease that is a balance between virus and host immune response, the gold standard to determine immune response are CD4 and CD8 T cell response levels, however conducting tests on these are difficult and expensive, especially for high endemic areas. Alternatively, the hepatitis B Core antibody (anti-HBc) titre can be used as a surrogate marker. Higher anti-HBc levels have been shown to reflect higher immune response, and in a study looking the baseline anti-HBc levels at baseline in patients receiving treatment, higher anti-HBc titre levels were associated with HBeAg seroconversion (25).

1.7.3.3 Stopping NUC treatment

Long term treatment with NUC has been shown to suppress HBV replication, which as per the SA guideline, is expected by week 24 of treatment (4). In theory, lifelong treatment with NUC is necessary but this does still pose a substantial burden on the healthcare system (26). The concern with stopping treatment is the risk of clinical relapse and hepatic

decompensation. In a meta-analysis looking at chronic HBV in the era of extensive antiviral use, it was found that viral relapse is a universal risk across all treatment arms, but that sustained clinical remission with persistent HBsAg loss is possible. Rates of HbeAg seroconversion ranged from 20-90%, and was dependent on the duration of consolidation treatment (22).

Other studies investigated the use of novel biomarkers as determinants of treatment response to stop the use of antivirals. One such biomarker is hepatitis B core-related antigen (HBcRAg), which is a combination of HBeAG, anti-HBc and truncated precure protein (p22cr), whose levels correlate to cccDNA activity. One particular study found that in patients with suppressed HBV DNA levels, they had significantly lower levels of HBcRAg, and this inferred a lower risk of relapse in patients over a 4 year period (26). Whilst these new findings are exciting, these studies still need to be replicated in immune inactive carriers and have not yet been adopted in any major guidelines.

1.8. Conclusion

Chronic HBV is a significant contributor of mortality worldwide, and despite advancements in prevention strategies such as vaccination, it remains highly prevalent in endemic areas such as Sub-Saharan Africa. The WHO has embarked on a goal to eradicate all forms of viral hepatitis by the year 2030 (5). Whilst SA has made strides to meet the WHO goals, there is a paucity in data describing the natural history of chronic HBV patients in SA. This limitation creates a challenge in developing frameworks to develop better prevention and treatment policies (19). In this study, we aim to gain a better understanding of the natural history and risk factors for progression of chronic HBV in SA.

1.9. Objectives

a. Primary objectives include:

To describe the demographic characteristics of chronic HBV patients attending Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) GI Clinic between June 2015- Dec 2021

Secondary objectives include:

i. To describe the natural history of chronic HBV patients

a) To determine the prevalence of HBeAg positivity amongst chronic HBV patients attending this institution.

b) To determine the rate of seroconversion from HBeAg positive to HBeAg negative in treated and untreated HBV in patients attending CMJAH GI Clinic

c) To determine the rate of seroconversion from HbSAg positive to HbSAg negative in treated and untreated chronic HBV patients attending CMJAH GI Clinic

d) To determine the prevalence of HCC and risk factors to progression to HCC

e) To determine the prevalence of cirrhosis and risk factors to progression to cirrhosis

1.10 Methodology

1.10.1 Study design

This will be a retrospective study based on review of clinical records of chronic HBV patients over the age of 18 attending the CMJAH GI clinic between June 2015-Feb 2022.

1.10.2 Inclusion criteria

- Patients with chronic HBV defined as HbsAg positivity for >6 months.
- Patients over the age of 18

1.10.3 Exclusion criteria

- Patients attending the CMJAH GI clinic with less than 6 months of data will be excluded.

1.10.4 Study sample size

Due to the nature of the study, to make inferences regarding treatment and prognosis, a convenient sample size of at least 100 patient records would have to retrieved.

1.10.5 Study limitations

The quality of data will depend on the quality of patient record keeping and access. A small sample size in comparison to other studies of this nature might limit data interpretation. Some patients may not have been biopsied to exclude other confounding aetiologies for liver disease and cirrhosis. Limitation to resources may affect patient investigations and access to drug treatment. The occurrence of COVID-19 in the last year, may have limited certain patient investigations (endoscopy, radiology investigations etc).

1.11. Data collection

Data will be extracted from patient clinical records using a data collection sheet. See Appendix A. Consent to access these records will be obtained from the relevant heads of department at CMJAH (internal medicine & gastroenterology), as well as consent from the CMJAH CEO. To avoid the duplication of patient records, patient records will be given a unique serial number.

1.11.1. Data handling procedure

Data will be stored on a password protected laptop and will only be accessible to the researcher. Physical patient files will remain in the GI clinic and filed according to the clinic specific system in alphabetical order. All electronically captured data on RedCap will be password protected and accessible only to the research investigator and supervisors of the research. No patient identifiers will be used.

1.11.2. Data analysis

The assistance of a biostatistician will be engaged, and Stata 17 will be used. Descriptive statistics will be applied, where categorical values will be described by frequency, ratios, and percentage calculations. Parametric data (normally distributed) will be described by means and standard deviations. Non-parametric data (skewed data), by medians and interquartile ranges. Means between groups will be compared using the T-test, whereas medians will be compared using the Wilcoxon Rank Sum Test. Chi-squared test will be used to compare percentages and the Fischer exact test will be used should the chi-squared test be comprised.

Correlation analysis will be used to make correlation conclusions between variables, as will regression analysis.

1.12 Ethics

As patient medical records will be used and sensitive information will be handled such as HIV status, all patients' records will be assigned a serial number, to provide anonymity to the researcher and supervisors. Ethics approval from the university postgraduate committee will be applied for prior to the commencement of data collection

1.13 Timing

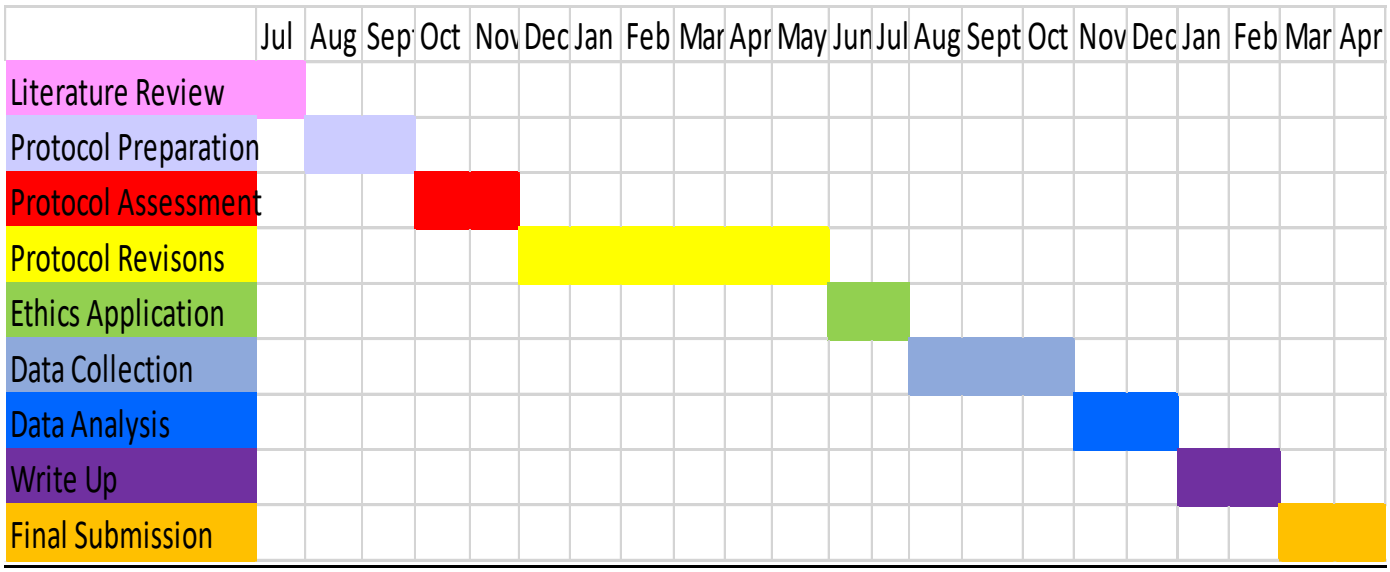

Figure 1: Project timeline.

1.14. Funding

The study will cost R10000. The foreseen costs include cost of administration such as printing costs, paper costs, binding, lamination, and transportation costs. This will be funding out of own pocket.

1.15. Bias

Referral bias may occur as this study is being conducted at a quaternary centre and usually patients with more advanced disease are referred here. Measurement bias may occur. To mitigate that, the entries into the data collection will be proofread. To avoid the duplication of patient records, each record entered on RedCap will be provided a unique serial number, where a patient's details and clinical records can be reviewed.

There is no investigator conflict of interest.

1.16. References

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Chapter Two

2. Submissible Article

A RETROSPECTIVE RECORD REVIEW OF CHRONIC HEPATITIS B PATIENTS ATTENDING A QUARTERNARY JOHANNESBURG HOSPITAL

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Conflict of interest

None

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2.1 Abstract

Background: Chronic infection with the hepatitis B virus (HBV) affects approximately 316 million persons across all ages worldwide with significant morbidity and mortality in endemic areas such as Sub-Saharan Africa. Despite advancements in our understanding and treatment of the disease, the epidemiology and natural history of chronic hepatitis B in South Africa is still poorly understood. In this study, we aim to describe this patient population in our quarternary level hospital.

Methods: A retrospective review of patient records was performed from September 2022 to June 2023 at our facility. Ninety-eight patients met inclusion criteria. Patient

demographics, risk factors, serology, comorbidities, confounding diseases, complications, and treatment modalities were captured.

Results: Our population had a male predominance (N=62; 63.25%), with the median age of diagnosis being 39 years (IQR 32-46). The prevalence of HBeAg positivity was 21.43% at diagnosis. The most prevalent clinical phase was HBeAg negative with chronic hepatitis (N= 58, 59.18%). HBeAg seroconversion occurred in 23.81% of the HBeAg positive patients,and in those who were HBsAg positive, 11.22% seroconverted. Cirrhosis was present in 30 patients, while 6 patients developed hepatocellular carcinoma (HCC). HBeAg positivity increased the risk of cirrhosis in multivariate models (p value= 0.043). Seventy-two patients were on treatment with low barrier resistance antivirals, with 90 patients having viral loads lower than detectable.

Conclusion The chronic HBV patient population attending this institution has similar demographics as other parts of the world. Patients attending our clinic have higher HBeAg and HBsAg conversion rates. A third of our cohort had cirrhosis, with a smaller subset having HCC. HBeAg positivity is a significant risk factor for developing cirrhosis and hepatocellular carcinoma.

2.2 Background

Chronic infection with the hepatitis B virus (HBV) affects approximately 316 million persons across all ages worldwide (1) and was responsible for 887 000 estimated liver-related deaths globally in the year 2015 (2). These statistics make it the most common chronic viral infection worldwide (3), with significant morbidity and mortality in endemic areas such as Sub Saharan Africa.

Untreated chronic HBV can result in cirrhosis and HCC. Documented risk factors for the progression to cirrhosis include HBeAg positivity, male gender, co infections with other viruses

such as hepatitis C and HIV, and confounding conditions such as Metabolic Associated Steatotic Liver Disease (MASLD) (20).

Despite advancements in primary prevention as well as treatment of the disease, it still poses a significant burden to the public health landscape of Sub-Saharan Africa. There is a paucity of demographic data in South African patients. Additionally, the natural history in these patients is less well established.

2.3 Methods

Objectives

The primary objective of the study was to describe the demographic characteristics of chronic HBV patients attending the Charlotte Maxeke Johannesburg Academic Hospital from June 2015 to February 2022.

The secondary objective was to describe the natural history of chronic hepatitis B in these patients from diagnosis at the facility to most recent follow up. This was achieved by establishing the prevalence of HBeAg positivity, the predominant clinical phase of chronic HBV, the rate of seroconversion for HBeAg, the rate of seroconversion for HBSAg and describing the prevalence of and risk factors for the progression to HCC and cirrhosis.

Data Collection

A retrospective review of patient records at CMJAH was performed from September 2022 to June 2023. One hundred and nineteen consecutive chronic hepatitis B (HBV) patients were identified, of which only 98 were deemed eligible for the study.

Patient demographics, risk factors, serology, comorbidities, confounders, and treatment modalities were then entered into the RedCap database. Once data collection was completed the data was independently analysed by a statistician.

Data Analysis

Descriptive statistics were applied, where categorical values were described by frequency, ratios, and percentage calculations. Parametric data (normally distributed) was described by means and standard deviations, with non-parametric data (skewed data), by medians and interquartile ranges.

Means between groups were compared using the T-test, whereas medians were compared using the Wilcoxon Rank Sum Test. Chi-squared test was used to compare percentages and the Fischer exact test was used where the chi-squared test was compromised.

Multivariate logistic regression was used to determine the predictors of HCC and cirrhosis. We presented the odds ratios and the 95% confidence interval. Statistical significance was considered at a p-value < 0.05. Stata Corp. MP Version 15 was used for computing the statistical data.

2.4 Results

2.4.1 Demographic Characteristics of Chronic HBV Patients attending CMJAH.

Of the 98 patients included in the study, 62 identified as males and 36 identified as females. The median age at presentation was 39 with an interquartile range of 32-46 years. Eighty-six of the study patients identified as black (87.76%). The most prevalent comorbidity in this cohort of patients was HIV, with 19 patients testing positive, followed by hypertension (n=8) and diabetes mellitus (n= 6).

Table 1: The demographics characteristics of chronic HBV patients attending Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) GI Clinic between June 2015- Dec 2022

Variable	***N (%)**
Age at presentation median (IQR)	39 (32-46)
Patients categorised by Age	
18-27	7 (7.14)
28-37	38 (38.78)
38-47	38 (38.78)
48-57	8 (8.16)
58-67	4 (4.08)
68-77	3 (3.06)
Sex	
Male	62 (63.27)
Female	36 (36.73)
Race	
Asian	1 (1.02)
Black	86 (87.76)
Coloured	4 (4.08)
Indian	2 (2.04)
White	3 (3.06)
Other	2 (2.04)
Associated Comorbidities	
Hypertension	8 (8.16)
Diabetes Mellitus	6 (6.12)
Increased abdominal circumference	3 (3.06)
Dyslipidaemia	1 (1.02)
HIV	19 (19.39)
Congestive cardiac failure	1 ((1.02)

*N Total = 98

2.4.2 Natural History of Chronic HBV Patients

Table 2: The Natural History of Chronic HBV patients at CMJAH

HBeAg Prevalence at Presentation	***N (%)**
HbeAg positive	21 (21.43)
HbeAg negative	77 (78.57)
Clinical Phases by EASL guidelines	
HbeAg positive with Chronic Hepatitis	17 (17.35)
HbeAg positive with Chronic Infection	4 (4.08)
HbeAg negative with Chronic Hepatitis	58 (59.18)

HbeAg negative with Chronic Infection	19 (19.39)
Seroconversion	
HbeAg positive to negative/HbeAg positive	5/21 (23.81)
HbSAg positive to negative/HbSAg positive	11/98 (11.22)
HB viral loads at last visit	
<2000 copies	89 (91.75)
>2000 copies	8 (8.25)

2.4.2.1 Prevalence of HBeAg and EASL Clinical Phases

Of the 98 chronic HBV patients included in the record review, 21 were HBeAg positive at time of presentation (21.43%). These patients were further classified into clinical phases according to the EASL guidelines. The most prevalent clinical phase was HBeAg negative with chronic hepatitis, with 58 patients, accounting for 59.18% of the patients included in the study. This was followed by HbeAG negative with chronic infection (N=19; 19.39%), HbeAg positive with chronic hepatitis (N=17; 17.35%) and lastly, HBeAg positive with chronic infection (N=4; 4.08%). The median ALT level across all clinical phases was 42 u/l, with an IQR of 26-67 u/l. In contrast, in patients who were HBeAg positive, the median ALT level was 58.5 u/l, with a IQR 42.5-177 u/l (p-value = 0.014).

2.4.2.2 Seroconversion of HbSAg

Eleven patients seroconverted from being HbSAg positive at first visit to HbSAg negative at last visit, demonstrating a 11.22% seroconversion rate in this population group. The median age at presentation in the seroconverted patients was 42 with an IQR 31-46 years. All patients who had HbSag seroconversion were HBeAg negative at last visit. The median ALT values were 67 u/l with a range of 20-963 u/l. Eight of these patients were on treatment, and all were virally suppressed at their last visit. Amongst the patients with HbSAg loss, six patients had cirrhosis, and one patient had HCC.

Table 3: Measured Variables in Patients with HbSAg Conversion

Variable	
Median Age at Presentation (IQR)	42 (31- 46)
HBeAg positivity [N (%)]	
At first visit	2 (18.18)
At last visit	0 (0.00)
Viral loads	
Median value at diagnosis (IQR)	106 copies (0 - 176000)
Median value at the last visit (IQR)	0 copies (0 - 200)
Treatment [N (%)]	
Yes	8 (72.73)
No	3 (27.27)
Cirrhosis	6 (54.55)
HCC	1 (9.09)

2.4.2.3 Seroconversion of HbEAg

Seroconversion of HBeAg occurred in 23.81% of the total study population (N=98). The median age at presentation in these patients was 33 (IQR 30-49 years). The median ALT value was 43 u/l with a IQR 23-2000 u/l. The median viral load was 164976 copies (IQR 16619-580000). All 5 patients who achieved HBeAg seroconversion were on treatment and virally suppressed at last visit. Five patients had cirrhosis, and one had HCC as well as cirrhosis.

2.4.3 Complications of Chronic HBV

2.4.3.1 Extrahepatic Manifestations

Extrahepatic manifestations were reported in 5 of the 98 patients (5.1%), with musculoskeletal manifestations such as arthralgias and arthritis being the most common.

2.4.3.2 Hepatocellular Carcinoma & Cirrhosis

Hepatocellular carcinoma (HCC) was seen in 6 of the 98 patients (6.12%), with 4 of the patients being HBeAg negative. All patients diagnosed with HCC were diagnosed by imaging modalities. The diagnosis of cirrhosis was made in 30 patients (30.61%). The diagnosis of cirrhosis was made by a combination of clinical findings and imaging.

2.4.3.4 Clinical Phases of Chronic HBV in Patients with HCC & Cirrhosis

The most prevalent clinical phase in the subset of patients with HCC and cirrhosis was those who were HBeAg negative with chronic hepatitis, with 3 out of 6 HCC patients and 17 out of 30 patients falling in this category, respectively.

2.4.4 Progression to HCC and Cirrhosis

2.4.4.1 Correlation of risk factors for HCC

Variables such as age at diagnosis, sex, HBeAg positivity, a history of hepatitis flares and the HB viral load at diagnosis, were applied into logistic regression models to assess risk factors for the development of HCC in the presence of chronic HBV infection. Males were 1.14 times more likely to develop HCC in comparison to females, however this was not statistically significant (p=0.685). Patients who were HBeAg positive at diagnosis were nearly 2 times more likely (1.89) to develop HCC in comparison to those that were HBeAg negative. In patients who recorded hepatitis flares, they were 1.59 times more likely to develop HCC. All these variables were placed into a multivariate model, where HBeAg positivity at diagnosis was the most crucial risk factor in developing HCC, with a odds ratio of 2.65, however not statistically significant (p value= 0.376).

Table 4: Univariate and multivariable logistic regression models exploring the risk factors associated with HCC among patients with chronic Hepatitis B.

Variable	Univariate OR 95% (CI)	P-value	Multivariate OR 95% (CI)	P-value
Age at presentation	1.04 (0.97- 1.11)	0.287	1.05 (0.97-1.13)	0.253
Sex				
Male	1.14 (0.20-6.55)	0.885	0.67 (0.09-4.71)	0.685
Female	1.00		1.00	
HBeAg at diagnosis				
No	1.00	0.479	1.00	0.376
Yes	1.89 (0.32-11.14)		2.65 (0.31-22.95)	
Hepatitis				
No	1.00	0.678	1.00	0.758
Yes	1.59 (0.18 - 14.39)		1.45 (0.14-15.53)	
HB viral load				
<2000 copies	1.00		1.00	0.803
>2000 copies	1.83 (0.29-11.47)	0.519	1.31 (0.16-10.61)	

2.4.4.2 Correlation of risk factors for Cirrhosis

Risk factors for the development of cirrhosis such as age at diagnosis, sex, HBeAg positivity at diagnosis, presence of hepatitis flares and confounders of cirrhosis were placed in a univariate and multivariate logistic regression model. HBeAg positivity was associated with cirrhosis. The odds of cirrhosis were greater with increasing age (p-value = 0.006). Metabolic Dysfunction-associated steatotic liver disease (MASLD) was prevalent in 12.24% of the study population (n= 12). Those with MASLD had decreased odds of developing cirrhosis with an OR of 0.06; 95%CI 0.00-0.81. (p-value=0.034). Among the HIV co-infected patients in this study, 5 had cirrhosis (26.31%), and all were virally suppressed, with a range of HB viral loads 0-27. Patients with co-infection with HIV had decreased odds of developing cirrhosis with an OR 0.76 (p-value = 0.628).

Table 5: Univariate and multivariable logistic regression models exploring the risk factors associated with Cirrhosis among patients with chronic Hepatitis B.

Variable	Univariate OR 95% (CI)	P-value	Multivariate OR 95% (CI)	P-value
Age at presentation	1.04 (0.99-1.08)	0.087	1.09 (1.03-1.17)	**0.006**
Sex				
Male	2.36 (0.89-6.26)	0.085	1.37 (0.43-4.38)	0.591

Variable	Univariate OR 95% (CI)	P-value	Multivariate OR 95% (CI)	P-value
Female	1.00		1.00	
HBeAg at diagnosis				
No	1.00	**0.019**	1.00	**0.043**
Yes	3.3 (1.21-8.98)		3.39 (1.04-11.07)	
Hepatitis				
No	1.00	0.116	1.00	0.165
Yes	2.57 (0.79-8.37)		2.74 (0.66-11.43)	
HIV				
No	1.00	0.628	1.00	0.861
Yes	0.76 (0.25-2.34)		1.13 (0.27-4.71)	

2.4.5 Confounders in Chronic HBV Infection

Other Conditions which may result in liver cirrhosis and hepatocellular carcinoma were recorded. One patient was co-infected with hepatitis C. Other conditions such as alcoholic steatohepatitis, autoimmune hepatitis, primary sclerosing cholangitis and primary biliary cirrhosis were present in this study cohort, but they were not statistically significant.

Table 6: Confounders in Chronic HBV Infection

Confounder	N (%)
MAFLD	12 (12.24%)
Alcoholic Steatohepatitis	4 (4.08%)
Autoimmune hepatitis	3 (3.06%)
Primary Sclerosing Cirrhosis	4 (4.08%)
Hepatitis C	1 (1.02%)
Primary Biliary Cirrhosis	1 (1.02%)
Toxins	2 (2.04%)
Other	6 (6.12%)

2.4.6 Treatment of Chronic HBV

Of the patients included in our study, 72 of the 98 (73.47%) were on treatment, and all of which, on antivirals. Most patients on antivirals were on TDF, a low barrier resistance antiviral. Two patients involved in this study were transplanted, however, they acquired chronic HBV post transplantation, and it was not the indication for their transplantation.

3. Discussion

Chronic HBV is the most common chronic viral infection worldwide (3) with a high prevalence in Sub Saharan Africa. It has a higher prevalence in males than in females (6). Similarly, in this study of 98 patients attending the CMJAH liver clinic, the demographic pattern showed that there is a greater proportion of males with chronic HBV in comparison to females, furthermore, an overwhelming number of patients were identified as black in ethnicity (87.76%), a reflection of the population of patients attending CMJAH.

In other studies conducted in SA, the age group with the highest prevalence was found to be between 15-49 year olds (6), in our study population group patients aged 28-37 years where the most prevalent, with median age of presentation, 40 years (and an interquartile range 33-45). In Samsunder et al's study into the seroprevalence of HBV, there was a prevalence of 1.1% and 0.9% of chronic HBV in males and females, which was attributed to the failure of immunization programmes. It is of interest that the age group with the highest prevalence was 28–37-year-olds in this study, as well as most patients in the study cohort under the age of 40, which might infer failure of primary prevention strategies, as this cohort would have qualified for vaccination.

Chronic HBV is defined as the persistence of HbSAg for six months post primary infection (2). All 98 patients in this study were HbSAg positive at diagnosis. HBeAg positivity correlates to patient infectivity (4). Of the 98 patients used in this study, 21.43% were HBeAg positive compared to 78.57% that were HBeAg negative at diagnosis. This is similar to the large study conducted by the HBRN across 21 centres, which showed that 78% of the 1625 patients were HBeAg negative at baseline (14).

Historically, chronic HBV is divided into 5 clinical phases, which do not occur linearly, based on HBeAg positivity, HBV DNA levels and the ALT levels (4). These parameters help to prognosticate the clinical course of patients. Hepatitis flares had been recorded in 75 of the 98 patients (76.53%) and at first visit 44 patients had HBV viral loads >2000 (44.90%). Within the HBRN network study cohort, 13% of patients did not meet any criteria for any defined clinical phase (14). The most prevalent clinical phase in our study was HBeAg negative with chronic hepatitis, which occurs more commonly in older men. This phase has been shown to have significant levels of necroinflammation and progressive fibrosis (4). Knowing which clinical phase is most prevalent has implications on decisions regarding treatment. That is to say, prior to patients presenting with established complications of chronic infection, the early initiation of therapy in males with high ALT values and repeated hepatitis flares, although HBeAg negative, may slow progression to HCC and cirrhosis.

At diagnosis 21.43% of the patients were HBeAg positive, five patients seroconverted, providing a 21.80% seroconversion rate in this cohort. Regarding functional cure, 11.2% of the patients in this study achieved HbSAg seroconversion. Factors that that may play a role in seroconversion have been looked at in other studies, and these include looking at other serological markers and their role in determining seroconversion. In our study population, we found that 76.53% had experienced hepatitis flares characterised by a raise in ALT levels, and there are studies which suggest that ALT flares are associated with HBeAg loss and suppression of HBV viral load without HBsAg loss (24). This may account for the high rate of seroconversion amongst our HBeAg positive patients in this study. The role of treatment in seroconversion cannot be undermined, with 72 of the 98 patients on treatment (73.47%). All these patients were on an antiviral with a low barrier of resistance.

Known complications of chronic HBV infection include extrahepatic manifestations, HCC, and cirrhosis. Due the limited record keeping, the evidence of extrahepatic manifestations was low, with only 5.10% of patients recorded as having them, with arthritis and arthralgia being the most common, while in other comparative studies, renal manifestations is the most prevalent extrahepatic manifestation (15). However, to make this diagnosis, renal biopsies are required exhibiting the presence of HBV immune complexes. As this was not an objective of this study, reliance on patient records for the identification of extrahepatic manifestations was used, and so it may be plausible that these were underreported.

HCC was present in 6.12% of patients, with 4 of these patients being HBeAg negative. All patients with HCC were diagnosed via imaging modalities, including contrasted tomography (CT) and magnetic resonance imaging (MRI). An even cheaper and less labour-intensive tool for screening is serial AFP measurements. The SA guidelines advocate for 6 monthly AFP measurements, together with abdominal ultrasound for surveillance (4). Patients with HCC in this study had AFP values 33 times higher than those without HCC. This illustrates that AFP monitoring remains a useful and cost-effective tool in identifying HCC in chronic HBV patients. HBeAg positivity was the risk factor the most associated with HCC, in both the univariate and multivariate models. Preceding data looking at the role of HBeAg positivity is conflicting, with the presence and absence of HBeAg being both a risk factor for HCC and in some studies not. This data set is very small, and so inferences cannot be made to the general population, and this calls for more and larger studies into HCC patients specifically, to see whether this data is reproducible in our context.

In the study conducted, 30 of the 98 patients (30.61%) have cirrhosis. It has been reported that in endemic areas, between 12-30% of chronic HBV patients can develop cirrhosis, in comparison to 6-15% developing HCC (10). Within our study cohort, cirrhosis was more

prevalent than HCC, much like in existing literature. The odds ratio of developing cirrhosis was up to 3.3 times higher in HBeAg positive patients compared to HBeAG negative patients (p-value=0.019). This differs from existing evidence which states that HBeAg positivity is associated with active viral replication, prolonged replication phases and prolonged periods of necroinflammation, resulting in clinical progression (10), however this may be biased by the overwhelming prevalence of HBeAg negativity in our study subset. When adjusted for the multivariate model, looking at age of diagnosis, sex, viral load at diagnosis, HBeAg positivity, highest ALT, the odds of cirrhosis increased with an increase in age (p-value=0.065), but HbeAg positivity was 3 times more likely to result in cirrhosis (p-value=0.041).

Besides the role of serology, there are other co-morbidities which have been shown to accelerate the clinical progression of chronic HBV, such as MASLD and co-infection with HIV.

While there is fair documentation of how chronic HCV rapidly progresses to cirrhosis with higher viral loads and poor response to treatment in the presence of MASLD (20), data on chronic HBV is still not conclusive. In a study produced in Hong Kong, 13% of the 1466 patients had metabolic syndrome, with 24% of these exhibiting definitive fibrosis on biopsy (20). Fibrosis was more frequently associated with hypertension and type 2 diabetes (20). Of interest in this study, the most prevalent comorbidity was hypertension (N=8;8.16%). Criteria for metabolic syndrome was met amongst 12% of the patients, but MASLD was not associated with the development of cirrhosis. This however does not conclude this argument, as the basis of MASLD was made based on patient records in this study, and no patients in this study were biopsied due to resource constraints. This may yield some importance in future, as the recognition and management of metabolic syndrome may reduce the risk of progression to fibrosis (20).

It has been proven that HIV co-infection alters the natural course of chronic HBV infection, resulting in higher levels of HBV viraemia, more frequent episodes of relapse and more rapid progression to liver fibrosis and HCC (3). In this study, 19.39% of patients were co-infected with HIV. HIV co-infected patients in this study had decreased OR of developing cirrhosis, and they were all virally suppressed on antiviral treatment. Whether these patients acquired HIV prior to their chronic HBV diagnosis and were therefore on treatment, is difficult to know as the data collection tool did not account for that, but it illustrates the value of treatment during HIV and HBV co-infection. However, SA has clear and frequently updated treatment guidelines for HIV infected patients, which also considers the treatment of other non-communicable disease, such as hypertension and diabetes, which may be risk factors for the development of cirrhosis.

Of the patients included in our study, 72 of the 98 (73.47%) were on treatment, and all of which, were on antivirals. Most patients on antivirals were on TDF, a low barrier resistance antiviral. All patients on treatment were virally suppressed, in addition to 17 patients who were treatment naïve with lower than detectable viral loads. Low barrier resistance antivirals are effective and a cost-effective treatment in our setting. Due to the study design being a cross-sectional study, we were not able to determine the timing to viral suppression, and whether considerations to stop NUC treatment can be instituted in this study population. Despite treatment, six of the patients with HbSAg seroconversion still had cirrhosis, and one patient on treatment had HCC. These patients may have initially presented with features of cirrhosis and HCC, as the nature of the study did not allow for time correlation to complications.

4.0 Conclusion

Chronic HBV is a common viral infection which can result in significant morbidity and mortality. It should not be looked at in isolation however, as it is a dynamic and complex disease process, influenced by host factors and immune factors. Understanding how it behaves within a population group provides

more targeted implementation of health policies to reduce its significant clinical burden. Within this study cohort, most patients were HBeAg negative with chronic hepatitis, which speaks to the immune response of hosts in the presence of chronic infection. Whilst our last published SA guidelines initiate therapy for patients who have had clinical decompensation, the findings in this study suggests that patients without a history of decompensation but with ALT flares, should be commenced on therapy.

Treatment modalities with low barrier resistance antivirals offers good viral suppression and should be employed even in asymptomatic patients. More research into treatment endpoints should be employed, but seroconversion of HBeAg and HbSAg is possible. HBeAg positivity was the most significant risk factor for the development of both cirrhosis and HCC in this population, further highlighting the importance of aiming for HBeAG seroconversion in newly diagnosed patients. Other risk factors for the development of cirrhosis such as MASLD and HIV, which are increasingly prevalent in our context, need more exploration. The findings in our study was underpowered to make any inferences. However, we know that both these conditions have been proven in other population groups to accelerate the development of cirrhosis. In areas where biopsies are not easily available biochemical measurements and other non-invasive modalities such as transient elastography should be used to screen for these conditions.

Chronic HBV remains a complex disease entity, but there is certainly hope on the horizon should better early adult screening programmes be implemented, and the early initiation of cost-effective low barrier resistance antiretrovirals. Should the above be instituted, we are likely to see greater rates of seroconversion and lowered prevalence of cirrhosis and HCC.

5.0 Study limitations

The study was done on a small cohort of patients, and based on limited patient records, which in turn did not provide enough data on patient risk factors, and due to resource constraints,

invasive procedures such as biopsies were not frequently performed to support diagnosis. Patient demographics may also have been influenced by the immigrant population attending CMJAH, and so while it gives a cross-sectional view of chronic HBV in Johannesburg, it may not reflect the true South African population, as data collection did not differentiate based on nationality. The study was done on patients attending a specialist clinic, and so they are likely to have more advanced disease than the general chronic HBV population, which in turn could result in inflated prevalence of cirrhosis and HCC. Whilst this study determined the prevalence of complications such as cirrhosis and HCC, the study design did not allow one to determine when these complications would occur post diagnosis, and in addition to this, one could not determine the rate at which seroconversion occurred.

6.0. Recommendations

Early detection of chronic HBV is required, to initiate early therapy in patients. This could be achieved by screening using ALT levels, which is more cost effective than serology markers, as we have seen that the most prevalent clinical phase is HBeAg negative patients with chronic hepatitis. Despite treatment and seroconversion, patients still developed cirrhosis and HCC, prospective studies looking at the rate of seroconversion and time to develop of complications would be useful in determining how to implement screening strategies for the broader population. The role of HIV and MASLD still remains inconclusive, studies looking specifically at HIV co-infected patients, and patients with the diagnosis of MASLD based on objective measurements, may provide greater understanding

6. References

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7. Appendices

7.1 Appendix 1: Data Collection Tool

7.2 Appendix 2 : Ethics Certificate

7.3 Appendix 3: Turnitin Report