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FACTORS INFLUENCING TREATMENT OUTCOMES AMONG CHRONIC HEPATITIS B PATIENTS ATTENDING THE KORLE-BU TEACHING HOSPITAL.

BY

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DECLARATION

I, Adwoa Afrakoma Agyei-Nkansah, declare that under the guidance of my supervisor, Prof. Kwasi Torpey, School of Public Health, University of Ghana-Legon, this dissertation is my original work, except for related works that have been duly referenced, and that no form of it has been presented elsewhere for another degree.

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PROF KWASI TORPEY

(SUPERVISOR)

DEDICATION

I dedicate this paper to my beloved husband John Nkansah and my children Jason, Aelish and Kwadwo. To John, I cherished but you perished and to Kwadwo whom this paper would have been done two months earlier. To coffee and sugar, you were the linchpin to my success.

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ABSTRACT

Background:

Hepatitis B is a major public health challenge and WHO is making all efforts at eliminating it as a public health threat by 2030. Elimination includes reduction of the reservoir of transmission through antiviral therapy. Sub-Saharan Africa is one of the regions of the world with high burden of disease. Treatment with antiviral therapy is almost unavailable and/or inaccessible. The study seeks to find factors affecting response to antiviral therapy in chronic hepatitis B (CHB) patients attending the Korle Bu Teaching hospital.

Aim

The aim of the study is to elucidate the factors that impact on treatment outcomes of chronic hepatitis B patients attending the Korle-Bu Teaching Hospital.

Methods:

A retrospective medical chart review was done using total enumeration sampling method from 2013 to 2018 in a teaching hospital in Accra. Data on CHB was abstracted based on eligibility criteria. Baseline parameters included sociodemographic, viral markers, liver biochemical test and pretreatment liver disease. A student t-test was used to determine changes in their pretreatment parameters. Binary logistic regression model was used to determine the effect of the independent variables on treatment outcome. Statistical analysis was performed using STATA version 15 at 95% confidence level.

Results: Seven hundred and eight patients' folders were reviewed. Average age of patients was 37.98 ± 10.52 years and averagely 33.08 ± 10.40 years at the time of diagnosis. Males were

relatively more than females (65.82%, 466/708). Over 50% (59.01%, 416/705) of the patients were married. Almost half of the participants had normal BMI (46.6%, 330/708). Three percent were co-infected with HCV (18/589) and 4% had diabetes (4.23%, 29/685). Fatty liver was present among 2.1% of the 677 patients with records. 5.4% of the 681 patients with records had preexisting liver disease. One-fifth of the patients were alcohol users (19.94%, 138/692). Of these, two-thirds of them drink >14 units/week (67.39%, 993/138). Less than a third of the patients were on treatment 30.5% (216/708) with over half having had treatment interruptions (52.8%, 114/216). One-fifth of the patients were HBeAg-positive (146/692) and 67.6% had undetectable HBV DNA (146/216). ALT and AST normalization occurred in over 50% ALT (55.8%, 87/156) and AST (53.5%, 157). HBeAg seroconversion was attained by 13.8% of 85 patients with such records. From the multiple logistic regression model, advancement in age at diagnosis, (AOR: 0.77, 95% CI: 0.61-0.97), male patients, (AOR: 0.30, 95% CI: 0.11-0.79), normal BMI, (AOR: 5.94, 95% CI: 1.91 - 18.48) significantly predicted viral suppression.

Conclusion

The proportion of patients on antiviral therapy was low among chronic hepatitis B patients at Korle Bu Teaching Hospital. Overall, younger age group, females, normal BMI were predictive of good viral and biochemical outcomes. None of the patients lost the HBsAg in this study.

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LIST OF ACRONYMS

Abbreviations

AFP	Alpha Fetoprotein
ALT	Alanine Aminotransferase
Anti HBe	Antibody To Hepatitis B E Antigen
ARV	Antiretroviral Therapy
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CAM	Complementary Alternative Medicine
CHB	Chronic Hepatitis B
CT scan	Computerised Tomography Scanning
HBcAb	Hepatitis B Core Antibody
HBeAb	Hepatitis B Envelope Antibody
HBeAg	Hepatitis B Envelope Antigen
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HBV-DNA	Hepatitis B Virus - Deoxyribonucleic Acid
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IFN	Interferon
IFN- α	Interferon- Alpha
IV	Intravenous
KBTH	Korle Bu Teaching Hospital
NUCs	Nucleos(t)ide Analogue
PEG-IFN	Pegylated Interferon
TDF	Tenofovir Disoproxil Fumarate
ULN	Upper Limits of Normal
USG	Ultrasonography

VL	Viral Load
WHO	World Health Organisation

CHAPTER ONE

INTRODUCTION

1.1 Background

Viral hepatitis B attacks the liver leading to either acute or chronic liver inflammation. It can lead to life threatening complications such as cirrhosis and liver cancer in adults. (Maucort-Boulch D, 2018). Hepatitis B virus is a DNA virus and affects the liver. It has a circular genome composed of partially double-stranded DNA. Although replication takes place in the liver, the virus spreads to the blood where virus-specific proteins and their corresponding antibodies are found in infected people. The virus is transmitted through contact with infected blood and bodily fluids (Caligiuri, Cerruti, Icardi, & Bruzzone, 2016). Viral hepatitis is a disease of public health interest with an estimated 257 million people chronically infected with the virus as at 2015 (World Health Organisation, 2017). According to Lemoine and other studies, 5-20% of the entire population of sub-Saharan Africa (80-100 million people) have evidence of Hepatitis B surface antigen (HBsAg) out of which an estimated 5% are at increased risk of developing fatal complications (Lemoine, 2014; Allain, 2016).

The WHO Western Pacific and Africa regions have the highest burden of people with HBsAg sero-positivity accounting for over 170 million of the population. This contributes to an estimated 70% of the global burden of the disease (WHO, 2018). The toll of Hepatitis B is heavy in Africa with sub-Saharan Africa being a highly endemic area with an associated high liver cancer burden (World Health Organisation, 2017). Ofori-Asenso found in their systematic review and meta-analysis, a prevalence of over 8% in Ghana (Ofori-Asenso & Agyeman, 2016). Hepatitis B has received very little attention compared to HIV despite the high burden, associated complications and high mortality.

The World Health Assembly and the WHO in 2014 set global targets to help eliminate Hepatitis B and C as a public health threat through prevention and treatment by 2030. The five key service areas involve prevention of mother to child transmission, universal implementation of birth dose hepatitis B immunization, reproductive health and infection control services, blood and injection safety and controlling other means of transmission (WHO, 2016). The past few decades have seen remarkable improvement in the clinical outcome of HBV patients, due to highly effective antiviral therapy (WHO, 2017). Active viral replication has been shown to be the main mechanism for poor clinical outcomes of hepatitis B. The goal of therapy is to eliminate or to permanently suppress viral replication thus reducing liver inflammation resulting in reduction of liver disease (Liaw, 2013).

Sustained viral suppression or hepatitis B surface antigen clearance is the ultimate aim of therapy to achieve survival and prevent complications. Antiviral induced viral suppression has led to significant improvement in both short – and long-term clinical outcomes of chronic hepatitis B infection. In some parts of the world where hepatitis B is highly endemic like Ghana, access to drugs is a big challenge due to lack of physical and financial access.

As part of the World Health Organization (WHO) efforts to eliminate hepatitis B as a global health problem by 2030, one of the priority areas for interventions of impact is quality treatment. This includes timely treatment initiation, patient and drug toxicity monitoring and looking for risk factors that may enhance liver damage and affect treatment outcomes such as alcohol use, herbal drug use, obesity, co morbidities and adverse drug reactions to achieve sustained viral suppression.

1.2 Problem Statement

Hepatitis B is globally one of the most common and severe infectious diseases resulting in significant morbidity and mortality (Franco et al., 2012). The presence of Hepatitis B surface antigen (HBsAg) determines infection (Hospital et al., 2005). Chronic infection is when the Hepatitis B surface antigen(HBsAg) persists for more than six months (Shapiro, 1993). It is estimated that 5% of adults exposed for the first time will develop chronic hepatitis B compared to children where 95% will become chronically infected (Scaglione & Lok, 2012).

Chronic hepatitis B infection if untreated can progress to acute liver failure, liver cirrhosis and eventually to liver cancer requiring liver transplant and other expensive treatment modalities such as microwave ablation (Taylor et al., 2009). Treatment is recommended only for chronically infected patients. The goals of treatment are to suppress viral replication thus preventing irreversible complications such as cirrhosis and liver cancer. Reduction in the amount of the virus as a result of antiviral therapy also results in reduction in transmission of the virus and improved patient survival and the quality of life (Baran, 2015). Several drugs have been shown to reduce the amount of the virus in the blood and this include tenofovir, lamivudine, entecavir and alpha interferon (IFN-α) (Duseja, 2019).

The burden of hepatitis B infection is however disparately distributed geographically with Africa being a continent with high endemicity. Sub-Sahara Africa (SSA) has over 8% of its population infected with the virus; with majority of them acquiring the infection through mother to child transmission. They also have a high burden of complications occurring in young adults. However, the cost of antiviral therapy is way above the reach of majority of these patients. In developed countries treatment is covered by insurance but not in Ghana. Data on patients' factors affecting

hepatitis treatment outcome is sparse in Africa with only Ethiopia reporting one-year treatment outcomes in their cohort (Desalegn et al., 2018) but non-existent in Ghana.

This study therefore sought to elucidate the proportion of patients on treatment and their outcomes and the factors affecting these outcomes. Ascertaining these factors, will help to optimise treatment goals and improve outcomes. It will help with policy formulation and assist in comprehensive care of patients with chronic hepatitis B infection.

1.3 Research Objectives

1.3.1. General objective

The aim of the study is to elucidate the factors that impact on treatment outcomes of chronic hepatitis B patients attending the Korle Bu Teaching Hospital.

1.3.2 Specific Objectives

- To determine the proportion of patients with chronic Hepatitis B on treatment
- To determine the treatment outcomes for patients with chronic Hepatitis B
- To identify factors influencing the treatment outcomes for chronic Hepatitis B patients

1.4 Research questions

1. What proportion of chronic hepatitis B patients needing treatment are on treatment?
2. What are the treatment outcomes for hepatitis B?
3. What prognostic factors influence the treatment outcomes for chronic hepatitis B patients?

1.5 Justification of study

The hepatitis B burden is very high, especially in sub-Saharan Africa (WHO 2016) where prevalence is over 12% among the adult population (Ott, 2015; WHO, 2017). It has also been

shown that the improvement in methods of detection of HBV, early diagnosis, better methods of treatment, and greater accessibility to, as well as acceptance of therapy have all helped to improve the survival of these patients**.** The antiviral therapy in conjunction with the improved survival has resulted in the decline in HBV related complications such as cirrhosis, end stage liver diseases and liver cancer. Of the over 250 million people with HBV, only 9% were aware of their diagnosis (WHO, 2017). In 2014, the World Health Assembly recognized viral hepatitis as a public health problem and called for governments and populations to act to prevent, diagnose and treat the disease (WHO, 2016). Despite the efficacy of antiviral medications, most people cannot access it due to the high cost and unavailability in some cases. One of the visions of the WHO is for all patients living with the virus to have access to safe, affordable and effective care and treatment (Spearman et al., 2017; WHO, 2016). The effectiveness of hepatitis B treatment has been well established. Antivirals are highly effective in serum DNA viral suppression and most have an excellent safety profile (Baran, 2015). Some factors have also been identified as affecting viral treatment outcomes including age, sex, use of alcohol, obesity in Europe, America and Asia (Aunget al., 2013; Heathcote et al., 2011; Lampertico et al., 2017). Currently there are few published data from Africa on normalization of ALT level and HBeAg seroconversion (Desalegn et al., 2018).

To date, no study has assessed proportion of patients with chronic hepatitis B achieving undetectable HBV DNA and factors affecting treatment outcomes in Ghana. It is therefore imperative to conduct a clinical audit of all patients who have or being treated for hepatitis B at the gastroenterology clinic to determine the treatment outcomes, as well as identify any associated predictive factors. Findings from this study will highlight the hepatitis B treatment outcomes among HBV patients in Ghana. Knowing the predictive factors may enhance patient selection with

better prognosis and will also serve as a guide to clinicians with respect to the appropriate timing of and treatment of these patients. Ultimately, findings from the study will contribute to a more effective clinical management of these patients to improve outcomes.

1.6 Conceptual Framework

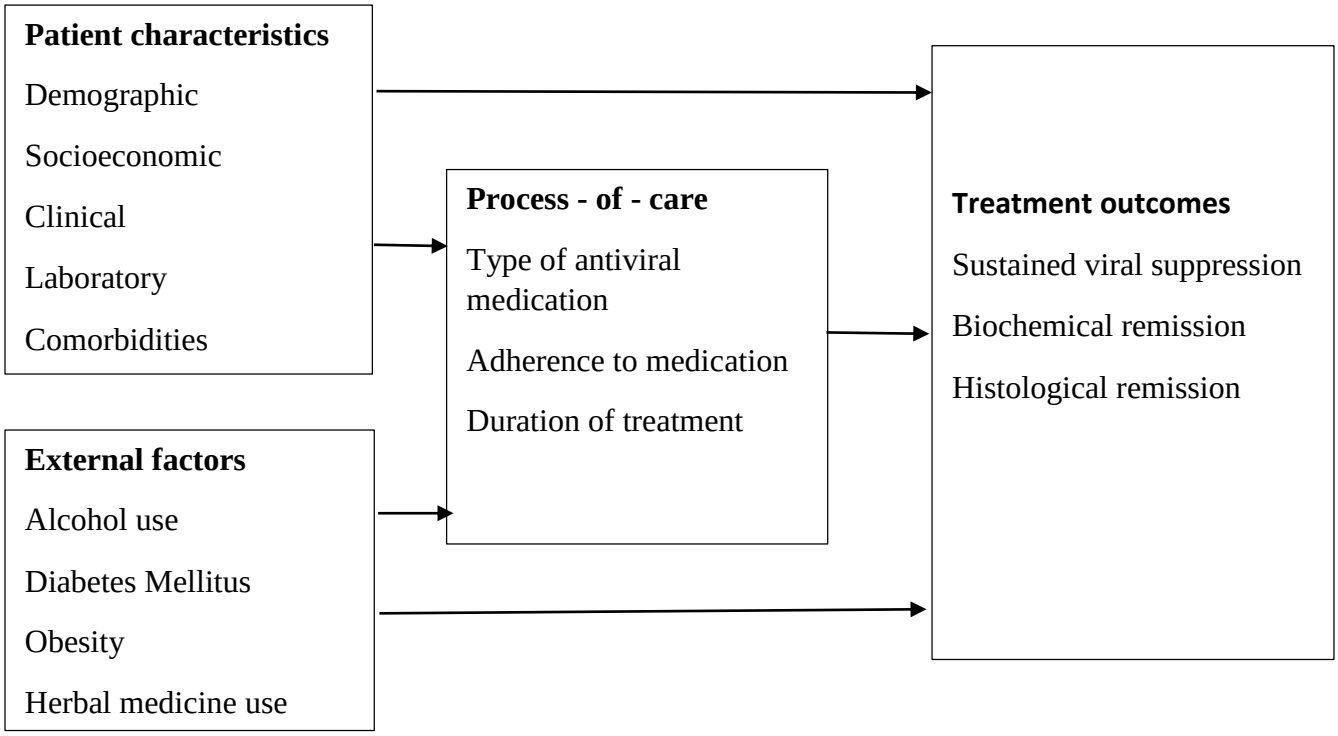

Figure: 1 Framework of Factors Influencing Treatment Outcomes in Patients with Chronic Hepatitis B.

Narrative Summary

This framework attempts to explain the influence of various factors on the treatment outcomes of chronic hepatitis B. Hepatitis B viral suppression, which is the outcome of interest is associated with significant reductions in HBV related liver complications like chronic liver disease, cirrhosis and liver cancer. Although treatment with antiviral therapy will reduce morbidity and mortality associated with the disease, other factors such as type of medicines, adherence to medications,

stage of liver disease and other sociodemographic factors may affect hepatitis B treatment outcomes.

Worldwide, socio-demographic characteristics have been found to influence health outcomes in both resource rich and resource limited countries. This framework demonstrates how age of the patient can influence treatment outcomes. It's been documented that older people, patients with high viral load and advanced liver disease do not response well to interferon (Baran, 2015). Patients with kidney problems or impairment are at increased risk of side effects or tenofovir intolerance resulting in treatment interruptions and poor outcomes. The viral characteristics and underlying liver disease have indirect relationships to treatment outcomes. Co infection with hepatitis C increases the risk of developing liver related complications and may impair viral suppression compared to hepatitis B mono infected patients.

The antivirals have been found to effectively suppress the infection albeit not to the same degree. The oral antivirals have minimal side effects, easy to administer and are preferred first line treatment over the injectables because of their potency in viral suppression and high genetic barrier to resistance. The drugs have different mechanism of action and treatment outcomes. Lamivudine is very potent and safe, but its major limitation is its low genetic barrier of resistance. Some external factors like alcohol use can affect the pharmacodynamics of the medications leading to sub therapeutic levels that can impact negatively on treatment outcomes. Herbal use in a similar way can lead to drug-drug interactions with resultant increased drug toxicity and treatment interruptions that can result in poor outcomes. The risk of developing adverse drug reactions with treatment interruptions includes the concomitant use of alcohol and other hepatotoxic drugs. Obesity with its attendant fatty liver disease can also increase the progression to liver cirrhosis and

cancer and thus resulting in poor outcomes. Adherence to medications is the linchpin in treatment outcomes for hepatitis B.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Antiviral therapy is a lifesaving hope for many people around the world. The use of Antiviral therapy in patients with Chronic Hepatitis B infection has significantly reduced morbidity and mortality associated with the disease. Few hepatitis B endemic countries have access to these medications. Although, hepatitis B surface antigen clearance is the ultimate treatment goal for hepatitis, this is extremely low globally**.** Hepatitis B treatment outcomes are influenced by many factors, including viral, biochemical, sex, type of antivirals, co-infection with other viruses, alcohol use and treatment amongst others. It is not clear as to what factors influence treatment outcomes in the Ghana.

2.2 Epidemiology of chronic hepatitis B

Over 250 million people are chronically infected with the virus as at 2015 (WHO, 2017). This is however disproportionately distributed geographically. The highest prevalence of hepatitis B is seen in WHO Western Pacific and African regions. The Eastern Mediterranean, South-East Asia and the WHO European Regions have low prevalence ranging from 1.6- 3% and less than 1% in the US. A recent systematic review of studies published in peer review journals from 1995–2015 estimated the average prevalence as 12.3% in Ghana with majority of the studies involving blood donors (Ofori-Asenso & Agyeman, 2016). Rural dwellers also had a slightly higher prevalence (13.3%) compared to 12.2% in the urban dwellers. The alarming observation was the affected individuals being in their reproductive as well as productive age groups 16-39years (Ofori-Asenso & Agyeman, 2016). Transmission in high endemic areas is mainly vertical i.e. from an infected mother to the baby. With the high prevalence in women in their reproductive age group and no government policy on at- birth dose vaccine, despite the routine testing for HBV at the

ante-natal clinics in most African countries, including Ghana, the elimination of HBV as a public health threat may elude us.

2.3. Spectrum of Chronic Hepatitis B

There are two main types of CHB infection. These are the HBeAg-positive and HBeAg-negative chronic hepatitis. The HBeAg-positive hepatitis occurs when one is exposed to the infection in the early neonatal period from an infected mother(Hospital et al., 2005). The lack of immunity in the neonate leads to persistence of the HBeAg. One may lose the HBeAg as the immune system develops with age however most will persist. This type of hepatitis is associated with high viral load and a moderate to no elevation of the serum ALT. The high viral load makes them more infectious compared to the HBeAg negative hepatitis. HBeAg negative hepatitis is more common and usually associated with low levels of viral load and fluctuating ALT and increased risk of complications.

2.4 Consequences of chronic hepatitis B

Early exposure to the hepatitis B virus will result in about 95% of them being chronic carriers with or without associated active viral multiplication with persistence of the HBeAg (Kuriakose & Ittyachen, 2018). Some of the carriers of the virus will remain inactive without much liver damage whilst up to about 20% will develop cirrhosis and another 5% will be at risk of liver cancer each year (Franco et al., 2012; Kuriakose & Ittyachen, 2018). Globally, over 800,000 persons died as a result of viral hepatitis B; 300,000 dying from liver cancer and over 450,000 from liver cirrhosis (GBD, 2016). Liver cancer progresses rapidly, and since treatment options are limited, the outcome is in general poor. In low-income settings, most people with liver cancer die within months of diagnosis (Anthony et al., 2016; Zakharia, Luther, Alsabbak, Roberts, & Chb, 2018). A 10 year review of autopsies and cancer mortality in Ghana revealed liver cancer as the third leading cause

of cancer mortality in women and the first in men (Wiredu & Armah, 2006). A multicenter study conducted in six African countries including Ghana showed the median age for developing cancer to be 45years, with men having it earlier at age 43years and 48years for women impacting negatively on the work force in Africa (Anthony et al., 2016). Hepatic cirrhosis is the commonest liver disease causing death in Accra, Ghana (Blankson, Wiredu, Gyasi, Adjei, & Tettey, 2005).

2.5 Antiviral therapy

Over the past decades, there have been major improvement in the treatment of patients with chronic HBV using two main strategies. This is either by an injection or through oral antiviral medications. The injectables are the interferon α or pegylated interferon. They work by improving the immune system and also inhibit viral multiplication (Shu, Woo, Kwok, & Ahmed, 2017). Interferons e.g. Pegylated interferon(PEG-IFN) are associated with more HBeAg loss, viral suppression and loss of HBsAg and finite treatment period (Vallet Pichard & Pol, 2014). The interferons are more effective in less advanced liver disease, high aminotransferase levels and moderate levels of HBV DNA (Uhl, Fricker, Haberkorn, & Mier, 2014). Younger patients and females respond better to these interferons than males and older patients albeit greater side effects (Shu et al., 2017). The oral antivirals are the nucleos(t)ides (NUCS). They work by suppressing viral multiplication (Baran, 2015). Patients with advanced liver disease, high amount of virus in the blood, poor tolerance to PEG-IFN, and moderate elevation of alanine aminotransferase respond better to the NUCs than the injection. Several studies have shown that sustained viral suppression on NUCS is associated with diminished liver cancer risk and regression of fibrosis and cirrhosis (Lok, Zoulim, Dusheiko, & Ghany, 2017).They however have low resistant threshold. The two first line NUCs recommended by WHO are entecavir and tenofovir (Terrault et al., 2018; Vallet Pichard & Pol,

2014). These two drugs are effective and have a high resistance threshold The advantage with the orals is the ease of administration and the minimal side effects (Xie, Ma, Feng, & Wei, 2017).

2.6. Treatment Outcomes

Defining hepatitis B outcome is complex. Various studies have used one indicator as the endpoint whereas a few have used composite treatment outcomes. The ultimate goal of treatment is the eradication of the HBsAg indicating a clinical cure. However, a handful of patients, about 3-7% are able to achieve this depending on the medication used (Marco, Stefano, Ferraro, Almasio, & Bonura, 2005). In the absence of that, four treatment outcomes have been defined (Aung et al., 2013). These are complete virologic or DNA suppression of the virus, biochemical or Alanine transaminase (ALT) normalization, histological improvement and loss of HBeAg. Viral suppression is when the amount of the virus in the blood is below <20IU/ml or undetectable level (Mamani, Majzoobi, Eini, & Keramat, 2014). Sustained suppression of the virus leads to decline in HBV related morbidity and mortality; and reduced risk of viral transmission (Duseja, 2019).

ALT is a standard surrogate for HBV activity. Inflammation of the liver is associated with elevation of the ALT. The mechanism of liver injury in HBV patients is through inflammation. Ongoing inflammation can lead to cirrhosis and ultimately lead to liver cancer (Taylor et al., 2009). Drug induced suppression of HBV-DNA is associated with normalization of the ALT and histological improvement (Duseja, 2019). Reduced liver inflammation is also associated with histological improvement of the liver. Ultimately if there is sustained viral suppression and ALT normalization, patients with HBeAg-positive hepatitis may become HBeAg-negative (Aung et al., 2013; Desalegn et al., 2018; Heathcote et al., 2011). The loss of HBeAg significantly improves survival and has been a primary goal for HBeAg positive hepatitis patients (Kau, Vermehren, & Sarrazin, 2008; Mamani et al., 2014).

2.7 Factors Affecting Treatment Outcomes

2.7.1 Viral factors

HBeAg status

Various factors have been found to predict treatment outcomes in chronic hepatitis B patients. These include viral factors such as the presence or absence of HBeAg, level of virus (HBV-DNA) in the blood and the presence of co-infections with either hepatitis C and/or HIV. Clinically, the goal of HBV therapy is to prevent progression to cirrhosis, liver failure and liver cancer through a sustained viral suppression. HBeAg-positive hepatitis is associated with very high levels of virus in the blood and low ALT levels. Thirty percent (30%) of HBeAg positive patients in a study showed virologic and histological response (Wong et al., 2016). On the contrary, Aung et al. found in their study, better response in HBeAg-negative patients on NUCS (Aung et al., 2013). A Canadian study after 144 weeks of therapy, also found a better response in patients with HBeAg negative hepatitis (87% compared to 71% of HBeAg-positive patients) (Heathcote et al., 2011). In HBeAg negative patients, younger age and female gender were significantly associated with treatment response (Xu, Liu, Farazi, & Wang, 2018). A multicenter study involving 19 countries in Europe, found 68% of HBeAg-positive patients and 90% HBeAg-negative patients treated with tenofovir having undetectable viral load after 12 months (Lampertico et al., 2017).

HBV-DNA levels

High levels HBV-DNA are associated with increased negative clinical outcomes such as liver failure, cirrhosis and liver cancer. Pretreatment HBV-DNA level is an independent predictor of efficacy of antiviral therapy including serum ALT normalization, loss of HBeAg and histological

outcomes (Hospital et al., 2005). Low levels have been found to be associated with better outcomes compared to high levels (Cho et al., 2017; Mommeja-marin, Mondou, Blum, & Rousseau, 2008). Other clinical trials have suggested a lower pretreatment HBV DNA level was predictive of HBeAg loss or seroconversion as well as viral suppression in patients receiving antiviral therapy (Lampertico et al., 2017; C. Lin & Kao, 2013; Sheng et al., 2011).

Coinfections with other viruses

Hepatitis B and C share the common mode of transmission and co-infection is common. One virus may suppress the presence of the other or they may be co-dominant. Co-infection also increases the risk of adverse outcomes. Until recently treatment was by the use of pegylated interferon but currently direct acting antivirals are being used with viral clearance occurring in up to 98% of patients with hepatitis C (Kau et al., 2008). In patients with hepatitis B/C co infection, some clinical trials using pegylated interferon with ribavirin showed good treatment outcomes in HCV even after 5 years off treatment; however, that of active hepatitis B is unknown (Gidding et al., 2012).

2.7.2 Biochemical and histological factors

Elevated baseline transaminase is a reflection of on-going inflammation with resultant liver damage. Patients with high levels of these enzymes have increased risk of HBV-related complications but higher rates of loss of HBeAg in a couple of studies. Lai in his study concluded that the higher the level of ALT (5 times the upper limit of normal), the better the treatment outcome compared to ALT levels twice the upper limit of normal (Lai, 2003; Lok et al., 2017). Inflammation also leads to liver fibrosis which can negatively affect outcomes of the disease. Untreated fibrosis will progress to cirrhosis and liver cancer. Significant improvement in fibrosis occurs with therapy (Lin & Kao, 2013).

2.7.3 Body mass index

Body mass index determines whether a person is obese or not. It is calculated using the weight (kg) and height. Obesity is defined as a body mass index (BMI) greater than 24.9kg/m^2. Obesity can predispose to fatty liver disease, cirrhosis and currently one of the emerging causes of liver cancer and indication for transplant (Agyei-Nkansah, 2017). A Taiwan study of university students showed high amount of virus in the blood of obese patients compared to normal weight students. Significant viral load predisposes to complications of liver disease. Furthermore, obese patients have an increased risk of developing diabetes mellitus and its associated complications. Diabetes, insulin resistance and BMI ≥25 kg/m^2 had positive additive effects on significant HBV DNA levels (Chien-Hsieh, Jin-Shin, Jin-Chuan, Lee-Lan, Chun-Jen, 2011). An Ethiopian study however showed low body mass index as an independent predictor of mortality of patients on antiviral therapy (Desalegn et al., 2019).

2.7.4 Diabetes Mellitus

Most of the data regarding diabetes and viral hepatitis have been on hepatitis C with virtually none for hepatitis B. These two conditions are prevalent globally contributing to the double burden of infectious and non-infectious disease. Studies have been explicit on the high prevalence of diabetes in hepatitis C but not in Hepatitis B (White D, Ratziu V, El-Serag H, 2009). Egypt the country with the highest prevalence of hepatitis C, has diabetes mellitus prevalence of 25% (Elhawary et al., 2011). A US study showed HCV prevalence of 4.2% among diabetics compared to 1.2% among the non-diabetics; however, the prevalence of hepatitis B in diabetics was not significantly different from the non-diabetics (White, Ratziu, El-Serag, 2009). Chen also found a strong association between HCV and diabetes but not hepatitis B (Chen, Fang, Wang, & Kao, 2018). Poor

treatment outcomes for hepatitis C occurs more in diabetics but few studies on hepatitis B patients (Hammerstad, Grock, Lee, & Hasham, 2015).

2.8 Patient factors

2.8.1 Adherence

To achieve optimal treatment response, adherence is key. Patients on hepatitis B therapy depending on the type of medication used can be on it for a finite time (pegylated interferon) or may be lifelong in HBeAg –negative patients on NUCS. Treatment adherence have been shown to significantly improve treatment outcomes. Definition of adherence include adhering to the dosing, duration, and right timing of drug therapy. Poor adherence may be due to the patient stopping the medication or could be due to prescriber factors. The 80/80/80 rule has been used to determine adherence to interferon therapy. This is defined as more than 80% adherence to doses, consuming over 80% of the required dosage and more than 80% of the treatment duration (Weiss et al., 2010). A study by Xu et al., showed poor adherence to treatment with only a fifth being highly adherent and over 50% adhering poorly to their medications. Poor adherence was high in rural dwellers and people without cirrhosis. Reasons for poor adherence included medication cost, forgetfulness, fear of potential side effects and stigma (Xu et al., 2018).

2.8.2 Alcohol Use

Alcohol use and misuse is common with more than 18 million adults in the United States abusing alcohol. It also contributes to the first five causes of morbidity and mortality in Europe (Lin et al. , 2017; Xu et al., 2018). Alcohol consumption in Ghana is highest among the young males (Osei-Bonsu, 2017). Heavy drinking is defined by the United States National Institute on Alcohol Abuse and Alcoholism as consuming over fourteen units per week. Consumption of 20-30g of alcohol is

associated with increased risk of liver cirrhosis and liver cancer (Iida-ueno, Enomoto, Tamori, & Kawada, 2017). Alcohol is known to suppress the immune system and its use therefore will lead to increased viral replication with high viral loads. It also inflames the liver resulting in high levels of the liver enzymes ALT and AST (Lin et al., 2017). A Taiwan study showed increased risk of developing liver cancer in HBV patients who used alcohol compared to HBV and alcohol use (Taylor et al., 2009). Although antiviral therapy has been shown to reduce complications of HBV patients without alcoholism there is scanty data available on association between alcohol consumption and response to treatment (Lin et al., 2017). It can be postulated that excess alcohol could negatively impact on treatment response because of its ability to induce liver enzymes and increase metabolism of the drugs (Lin & Kao, 2013). Jang and co-authors in their cohort did not find significant effect on the treatment outcomes with entecavir (Jang et al., 2018; Taylor et al., 2009). Ayako however recommended strict alcohol abstinence in patients with chronic hepatitis B in their study (Iida-ueno et al., 2017).

2.8.3 Herbal medicines

Use of Complementary and alternative medicine (CAM) in Africa, China and Asia is a longstanding tradition. These drugs are used prior to visiting the hospital or concomitantly with orthodox drugs. Various reasons have been given with regards to its use. Some people think is safer, easily available and cheaper. Data on its use is lacking but several reports have been documented in its use in HIV. One study reported better improvement with concomitant use of antiviral therapy and CAM (UNAIDS & WHO, 2008). Drug-drug interactions as well as liver damage with herbal treatment may have the potential of reducing the efficacy of antiviral therapy.

2.8.4 Drug related factors and duration of treatment

Antiviral therapy has changed the clinical outcomes of chronic hepatitis B infection with patients living longer and having less complications. The major goal of therapy is to improve quality of life which can be realized if there is sustained viral suppression, induction of biochemical remission and histological improvement (Liaw, 2013; Sarin et al., 2016). Two main types of drugs have been approved for use by WHO in the management of chronic hepatitis B. These are the injectables (interferon α and pegylated interferon) and the oral nucleos(t)ide antivirals (tenofovir, entecavir and lamivudine etc.). The injectables act by suppressing viral multiplication and also boost the immune system of the patient to help fight the infection (Vallet Pichard & Pol, 2014). They are associated with better HBsAg clearance and loss of HBeAg compared to the orals. The other advantage is the finite duration of treatment (Wong et al., 2016). The nucleos(t)ide therapy inhibit viral replication but have no immune modulatory effect. They are preferred over the injectables due to good side effect profile and the ease of administration. The first line treatment recommended by WHO are tenofovir, entecavir or pegylated interferon. These oral antivirals are highly potent in viral suppression and have high genetic barrier of resistance see Appendix 2.

2.9 Sociodemographic characteristics and its effect on treatment outcome.

Hepatitis B and C treatment outcomes are determined by both viral and host factors. Host factors include the sociodemographic characteristics of the patient. Younger age has been observed to be significantly associated with treatment outcomes in studies done in Africa and other parts of the world (Aung et al., 2013; Desalegn et al., 2019; Gidding et al., 2012). Predictive factors identified in HBeAg –positive hepatitis who had been on interferon therapy for 2 years were older age and female gender. However, for the HBeAg-negative hepatitis female age was the significant predictive factor and not older age (Shu et al., 2017). Although antivirals are highly efficacious,

adherence plays a major role in the treatment outcomes. A Chinese study reported female sex as a predictive factor for drug adherence and treatment outcomes (Peng, Yin, Cai, Yu, & Zhong, 2015).

A study in India highlighted high cost as a hurdle in initiation and treatment of hepatitis B thus negatively affecting treatment outcomes indirectly. The ability to afford medications may depend indirectly on the level of medication and the occupation of the patient. Compliance is also better in the educated compared with the uneducated due to better understanding of the disease and its treatment, however, a counter-intuitive study on lupus patients showed a lower level of adherence to medication (MGross et al., 2014).

2.9 Conclusion

Lifelong effective antiviral agents against chronic hepatitis B infection have the potential to significantly reduce morbidity and mortality. Outcomes of treatment are viral suppression, histological improvement and ALT normalization. Timely treatment initiation, monitoring of patient and adverse drug reactions as well as complications will help optimize treatment. A variety of factors however have been postulated to impact on outcome.

CHAPTER THREE

MATERIALS AND METHODS

Introduction

This chapter explains the methods and procedures used to collect and analyze field data for the study. This section consists of description on the study area, research design, procedure for selection of participants, research instrument, data collection process, ethical considerations and data analysis process.

3.1 Study Area

The study took place at the Gastroenterology clinic of Korle Bu Teaching Hospital. Korle Bu is the largest hospital in Ghana with a bed capacity of 2000. It is located in the Greater Accra Region. It has a daily outpatient attendance of 1500. The Gastroenterology clinic sees people with gastrointestinal as well as liver and biliary diseases. It is manned by three liver consultants, two resident doctors and two interns on rotation at a time. It sees patients both from its catchment area and also serves as national referral hub for hepatitis B and other gastrointestinal and hepatobiliary diseases. The clinic has over 5,000 registered patients. The clinic provides both inpatient and outpatient care with inpatients being admitted to the medical ward. Outpatient clinic attendance averages 50-60 patients per clinic day. The clinic is held once in a week

3.2 Study Design

The study design was a retrospective chart review of all the chronic hepatitis B positive patients from 2013 to 2018. Medical records of chronic hepatitis B patients meeting the inclusion criteria were abstracted and multiple variables collected.

3.3. Study population

The study population were chronic hepatitis B patients (CHB) who were enrolled at the Gastroenterology clinic of the Korle Bu Teaching Hospital from 2013-2018.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

Patients with the following criteria were recruited into the study:

- Patients aged between 14years and 75years who have been confirmed to have chronic HBV infection with documentary evidence of having been on treatment for at least six months.

3.4.2 Exclusion criteria

Patients with the following characteristics were excluded

- Patients registered or enrolled before 2013 and after 2018.
- Patients with incomplete or missing data with respect to the studied variables
- HIV co-infected patients because they are treated at a different centre
- CHB patients with hepatocellular carcinoma and acute liver failure before the treatment
- Pregnant women
- Patients younger than 14years and older than 75years

3.5 Sample size estimation

Total enumeration method was used. Medical records of patients meeting the inclusion criteria were used. Data was collected on multiple variables at the Gastroenterology clinic of the Korle Bu Teaching Hospital.

3.6 Selection of medical records

At the Gastroenterology clinic of the Korle Bu teaching hospital, medical records of the unit were used to collate the medical charts of patients with chronic hepatitis B infection. The medical record charts served as secondary data. These charts had been compiled over many years. The data includes demographic, detailed examination reports, laboratory and imaging results. Data on patients with chronic hepatitis B defined as the presence of HBsAg for at least 6 months obtained using total enumeration. Further selection was based on the flow diagram in figure 2.

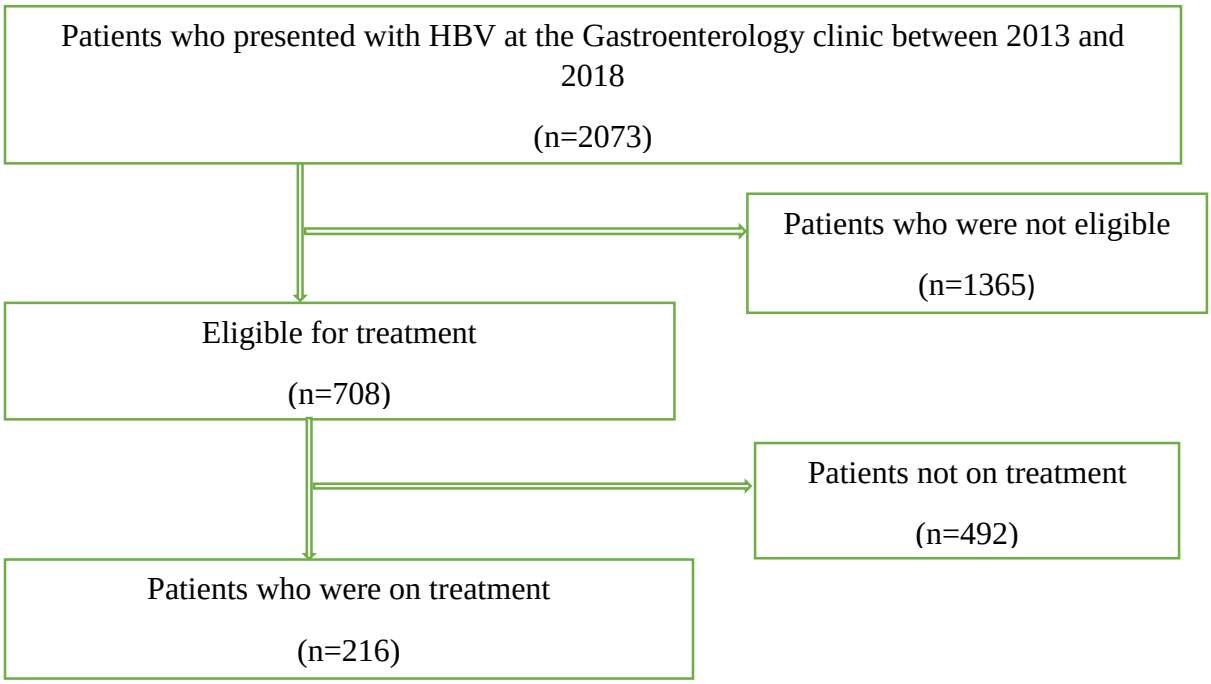

Figure: 2 Flow diagram for selection of patients with chronic hepatitis B

3.6.2. Data collection methods and tools

Prior to data collection, data abstractors were carefully chosen. In this study, medical residents and house officers were used for the abstraction. They were trained on how to use the tool and the various variables explained to them as in a similar study (Gearing, Mian, Barber, & Ickowicz, 2006). The abstractors were blinded from the study hypothesis to help reduce bias. In all, four

doctors were used for the data capturing. The extracted information was entered into a data base both manually and electronically using standardized medical terminologies. The abstraction tool was simple and was based on study objectives. The tool was made to logically follow the flow of information in the medical charts. A few medical charts were reviewed to ensure the collection tool was understood by all as a pilot. This helped finalize the data extraction form.

The database was an electronic version with drop down menus. The following data was abstracted and compiled into the database:

Socio demographic information	Age, Sex, Education, Occupation, Marital status,
Risk factors for acquiring Hepatitis B	Family history, blood transfusion, tattoos, IV drug use
Co morbid conditions	Diabetes, Hepatitis C, Alcohol use
Clinical symptoms & Signs	Pruritus, fatigue, anorexia, weight loss, abdominal pain, Ascites, portal hypertension, cirrhosis
Laboratory results extracted	Virologic parameters (HBeAg, HBeAb, HBV DNA Liver function Test (ALT, AST) Alpha fetoprotein (AFP), liver histology
Medical imaging results extracted	Abdominal ultrasound, CT Scan
Current Antiviral therapy regimen & duration on treatment	Tenofovir, Lamivudine, pegylated interferon, Entecavir
Treatment outcomes	HBV viral suppression, Biochemical remission, HBeAg seroconversion, HBsAg loss.

3.7.1 Variables

Dependent variables (Outcome Variable): The treatment outcome was categorized into three

i. Suppressed HBV DNA levels (<20IU/ml) using polymerase chain reaction

ii. Normalization of Alanine Aminotransaminase

iii. Loss of HBeAg

A composite treatment outcome was defined as suppressed HBV DNA, ALT normalization and loss of HBeAg in HBeAg positive patients.

Chronic hepatitis B is defined as positive hepatitis B serology (HBsAg) six months apart or positive serology for hepatitis B and the presence of Hepatitis B core antibodies (HBcAb).

Sustained viral suppression is undetectable viral load or load <20IU/ml. This is an acceptable virologic treatment outcome measurement according to current guidelines because, it is associated with reduced long term complications (GBD, 2016).

Biochemical remission occurs when serum alanine aminotransferase (ALT) is normalized defined as an ALT level less than 30 IU/L for males 19IU/L for females (Prati et al., 2002).

Independent variable- Factors influencing Hepatitis B treatment outcomes included age, male sex, income, family history of Hepatitis B, use of herbal medications, body mass index, alcohol use, diabetes, obesity, baseline ALT levels, viral loads, alpha fetoprotein, HBeAg, treatment regimen and treatment duration (See table 3.1).

Table 3.1: Definition of Variables and Their Scale of Measurement

Variable	Operational Definition	Type of variable	Scale of measurement
HBV DNA viral load	Undetectable HBV DNA viral load defined as HBV DNA<20IU/ml	Dependent	Binary/ Ordinal
On therapy ALT level	Serum Alanine aminotransferases (ALT) normalization is ALT level less than 30 IU/L	Dependent	Binary/ Ordinal
HBeAg serology	Disappearance HBeAg	Dependent	Binary/ Ordinal
Composite treatment outcome	Defined as undetectable HBV DNA viral load, ALT normalization, and HBeAg seroconversion	Dependent	Binary/ Ordinal
Age	Age at last birthday	Independent	Discrete
Family History	Whether the respondent has a first-degree family with the disease	Independent	Binary/ Nominal
Alcohol use	Quantity of alcohol taken in units	Independent	Ordinal
Pre-treatment ALT levels	Degree of pre-treatment ALT level above upper limit of normal	Independent	Ordinal
Pre-treatment serum HBV DNA viral load levels	HBV DNA >= 20,000IU/ml in HBeAg-positive* HBV DNA>= 2,000IU/ml in HBeAg- negative* (Liaw, 2013)	Independent	Ordinal
Pre-treatment HBeAg	Whether the HBeAg serology is positive or not	Independent	Nominal
BMI, kg/m^2 Index	Will be defined by a ratio of weight in kilogram and height in meters squared	Independent	Ordinal
Sex	Either male or female	Independent	Nominal
Liver disease stage	Presence of liver cirrhosis by scan, histology or APRI score	Independent	Ordinal
HCV status	Whether there is serological evidence of hepatitis C Antibody	Independent	Ordinal
Herbal medicine Use	Whether patient uses any form of herbal	Independent	Nominal
Antiviral treatment given	Type of antiviral drugs patient is on	Independent	Nominal
Treatment Duration	Date of start of antiviral therapy	Independent	Discrete

3.8. Statistical analysis

Data was analyzed using StataIC version 15 (64-bit) (StataCorp LP, College Station, TX, USA) for editing and analysis. Continuous variables were presented as mean and standard deviation whiles categorical variables were presented as counts and percentages. The mean values of biochemical parameters at baseline were compared with that after 6 months or more on antiviral therapy using the Students t-test. Qualitative and quantitative differences between subgroups were analyzed using chi square (χ^2) or Fisher's exact tests for categorical parameters and the student t test or Mann-Whitney U test for continuous parameters, as appropriate. For means between groups, in cases where data normality was violated, non-parametric tests including Mann-Whitney U test and Wilcoxon signed-rank were used. Data were also categorized according to whether the HBeAg was positive or not. In predicting independent factors which may be associated with the treatment outcomes, logistic regression model was used. Associations between independent variables and outcome variables were analyzed using univariate and multivariate analysis to determine predictors of treatment outcome. Significant level was set at a p- value of 0.05.

3.9. Quality control

Medical chart review is associated with inherent quality issues such as missing or incomplete data, wrongly captured data, difficult to interpret and inconsistent data, these were addressed to improve on study reliability and validity. A robust abstraction tool with training of abstractors helped to improve the quality of the data. In overcoming human errors from multiple abstractors, inter-rater reliability was done to improve reliability between multiple abstractors (Gearing et al., 2006). Weekly meetings were held for the abstractors to address any queries or concerns regarding the abstraction tool.

3.9. 1. Pretesting the study instruments

A pilot was carried out at the Korle Bu polyclinic using 10% of the overall sample size. This was to find out how easy and adequate the abstraction tool was. Modifications were made to overcome potential challenges (Gabel & Shindledecker, 1990; Wu & Ashton, 1997). For reliability of the data abstracted, two abstractors each were made to abstract same folder at different times. An abstractor was again made to rate twice the same medical chart at different times. The Cohens Kappa rating was then applied to determine reliability (Allison et al., 2000; Rosen, 1995). Variables that were not reliable were further assessed and abstractors trained.

The formula used to calculate Cohen's kappa for two abstractors (Reliability, Qualitative, & Coding, 2012) is as shown below.

$$\kappa = \frac{p_o - p_e}{1 - p_e} = 1 - \frac{1 - p_o}{1 - p_e},$$

Where: P_o = the relative observed agreement among abstractors. P_e = the hypothetical probability of chance agreement

The Kappa statistic varies from 0 to 1, where.

- 0 = agreement equivalent to chance.
- 0.1 – 0.20 = slight agreement.
- 0.21 – 0.40 = fair agreement.
- 0.41 – 0.60 = moderate agreement.
- 0.61 – 0.80 = substantial agreement.
- 0.81 – 0.99 = near perfect agreement
- 1 = perfect agreement

Acceptable level was near perfect agreement (0.81).

3.9.2 Data handling

Following final data abstraction and cleaning, personal identifying information were removed to contain only the study identification number and abstracted data that cannot be traced to the patient. Codes were assigned to research participants. Adequate and accurate records were maintained to enable the conduct of the study to be fully documented and the data to be fully verifiable. A copy of all source data and abstraction forms remained on site until the study was completed. The abstraction tools were securely kept. Electronic data were all password protected in the database.

Study Instrument

A data abstraction tool consisted of 40 closed and 6 opened questions based on study objectives. The tool captured sociodemographic features, HBV medical history, exposure characteristics, comorbid conditions, alcohol and herbal use, clinical features of liver disease, serological, biochemical and histological laboratory parameters; viral titers, imaging, antiviral medications, adherence and treatment outcomes. See appendix A.

3.9.3. Handling Missing Data

Missing data can introduce bias and make analysis very difficult. It can also impact negatively on the efficiency of the study. To overcome this, imputation was used to replace those missing values with estimated ones to avoid deleting important missing variables whose absence may affect the overall outcome.

3.10. Data Dissemination

The results of the study will be presented to the Department of Medicine and School of Public Health. Presentations of the outcome of this study will also be made at College of Health Science

Annual Scientific Conference and Research Forum. Manuscripts from this work will be published in reputable peer reviewed scientific journals.

3.11. Ethical consideration

3.11.1 Ethical approval

The study was submitted for formal review and approval to the Institutional Review Board of the Korle Bu Teaching Hospital because the dataset comprised of identifier secondary data. It was conducted in accordance with the ethical regulation of the Korle Bu Teaching Hospital-Scientific and Technical Committee/Institutional Review Board (STC/IRB) and the Helsinki Declaration on Human Experiments in 1964 (revised in 2000). Formal approval was obtained from Korle Bu Teaching Hospital-Scientific and Technical Committee/Institutional Review Board (STC/IRB). The study's registration ID no.is (KBTH-IRB) 000138/2018.

3.12. Limitations of the study

The main limitations with the study were incomplete documentation, missing data, incomprehensible information and ineligible handwriting. Some information could also not be verified because the blood test results were with the patient and not documented in the medical charts. Some patients also kept their folders with them and so were not available to be captured. Information on whether patient was taking alcohol was documented most of the time on just the first day of reporting.

CHAPTER FOUR

RESULTS

4.1 Demographic Characteristics of HBV patients at the KBTH

The study involved the review of 708 patients' folders. The average age of the patients was 37.98 ± 10.52 years as they are mostly diagnosed averagely at the age of 33.08 ± 10.40 years. The proportion of males was about twice that of females for all (65.8%, 466/708) and a little over 68% in those on treatment. More than half (59.0%, 416/705) of the patients were currently in a union (married/cohabiting) and 64% in the treatment group. Close to half of the participants were of normal BMI size (46.6%, 330/708). With regards to those on treatment, the average age at enrolment was 34.78 years. A little over 64% (319/216) of them were married. Forty four percent (44%) of those on treatment had had tertiary education. Details of participants' demographics are shown in Table 1.

Table 4.1: Demographic Characteristics of HBV patients at the KBTH

	Treatment		
	No, n(%)	**Yes, n(%)**	**Total, n(%)**
Current Age (Mean ± SD)	37.05 ± 10.27	40.04 ± 10.76	37.98 ± 10.52
Age at Enrollment (Mean ± SD)	34.14 ± 10.35	34.78 ± 10.60	34.34 ± 10.42
Age at Diagnosis (Mean ± SD)	32.79 ± 10.46	33.70 ± 10.25	33.08 ± 10.40
Marital Status			
Never in union	188(38.21)	71(32.87)	259(36.58)
Currently in union	277(56.30)	139(64.35)	416(58.76)
Formerly in union	27(5.49)	3(1.39)	30(4.24)
Missing	0(0)	3(1.39)	3(0.42)
Sex			
Female	174(35.37)	68(31.48)	242(34.18)
Male	318(64.63)	148(68.52)	466(65.82)
Ethnicity			
Akan	232(47.15)	114(52.78)	346(48.87)
Dagbani	60(12.2)	32(14.81)	92(12.99)
Eve	60(12.2)	25(11.57)	85(12.01)
Ga	52(10.57)	14(6.48)	66(9.32)
Hausa	78(15.85)	21(9.72)	99(13.98)
Non-Ghanaian	10(2.03)	7(3.24)	17(2.40)
Missing	0(0)	3(1.39)	3(0.42)
Education			
None	84(17.07)	17(7.87)	101(14.27)
Primary	110(22.36)	42(19.44)	152(21.47)
Secondary	160(32.52)	61(28.24)	221(31.21)
Tertiary	138(28.05)	96(44.44)	234(33.05)
BMI			
Mean ± SD	25.40 ± 5.20	25.30 ± 4.53	25.37 ± 5.00
Underweight	30(6.10)	6(2.78)	36(5.08)
Normal	222(45.12)	108(50.00)	330(46.61)
Over weight	149(30.28)	66(30.56)	215(30.37)
Class1 obesity	91(18.50)	36(16.67)	127(17.94)

SD: Standard Deviation, n: Frequency, %: Column Percentage

4.2 Distribution of the pre-treatment characteristics of the participants

Table 2 exhibits the distribution of the pretreatment characteristics of the participants. The percentage of patients with HCV antibody positive was 3.1% (18/589). Twenty nine out of the 685 patients with records on their diabetes status had diabetes (4.23%, 29/685). Fatty liver was present among 2.1% of the 677 patients with records. Clinical evidence of liver disease was present among 5.4% of the 681 patients with records. About one-fifth of the patients were alcohol users (19.94%,

138/692). Of the 138 drinking patients, most of them drink 14 or more units per week (67.39, 93/138). In the treatment group, liver disease was found in 1.4% (3/216). Sixteen percent (16%) had a history of alcohol, out of which approximately 50% had significant alcohol intake.

Table 4.2: Distribution of the characteristics of participants

	Treatment		
	No, n(%)	**Yes n(%)**	**Total, n(%)**
HCV Status			
Negative	390(79.27)	181(83.8)	571(80.65)
Positive	15(3.05)	3(1.39)	18(2.54)
Missing	87(17.68)	32(14.81)	119(16.81)
Diabetes mellitus			
No	456(92.68)	200(92.59)	656(92.66)
Yes	22(4.47)	7(3.24)	29(4.1)
Missing	14(2.85)	9(4.17)	23(3.25)
Fatty Liver			
No	461(93.7)	202(93.52)	663(93.64)
Yes	7(1.42)	7(3.24)	14(1.98)
Missing	24(4.88)	7(3.24)	31(4.38)
Liver Disease			
No	439(89.23)	205(94.91)	644(90.96)
Yes	34(6.91)	3(1.39)	37(5.23)
Missing	19(3.86)	8(3.7)	27(3.81)
Alcohol use			
No	378(76.83)	176(81.48)	554(78.25)
Yes	104(21.14)	34(15.74)	138(19.49)
Missing	10(2.03)	6(2.78)	16(2.26)
Units per week			
< 14	27(25.96)	18(52.94)	45(32.61)
>= 14	77(74.04)	16(47.06)	93(67.39)
Alcohol Type			
Single (Beer/Brandy/Whisky/Wine)	73 (70.19)	33(97.06)	106(76.81)
Combine (Beer/Brandy/Whisky/Wine)	31(29.81)	1(2.94)	32(23.19)
Use of Herbal Medicines			
No	375(76.22)	166(76.85)	541(76.41)
Yes	60(12.2)	14(6.48)	74(10.45)
Missing	57(11.59)	36(16.67)	93(13.14)

n: Frequency, %: Column Percentage

4.3 Proportion of patients on treatment

The proportion of patients who were on treatment was 30.5% (216/708) with more than half of them having had an interrupted treatment (52.8%, 114/216).

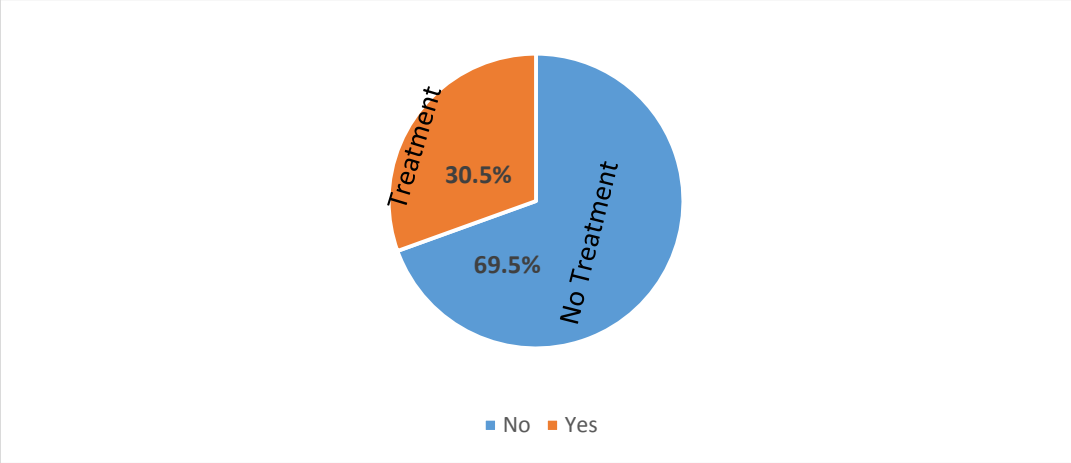

Figure 3: Distribution of treatment status of HBV patients at KBTH

4.4 Evidence of liver disease among HBV patients at KBTH

Among the patients with clinical symptoms and signs, 14.8% (89/603) of them presented with an enlarged liver and 5.2% (26/504) had their spleens enlarged. With the 506 patients with information on ascites, 12.5% of them had documented evidence of ascites. In all, only forty patients had information on their liver histology.

Table 4.3: Evidence of liver disease among HBV patients at KBTH

	Frequency	Percent
Liver		
Normal	450	74.63
Enlarged	89	14.76
Spleen		
Enlarged	26	5.16
Normal	478	94.84
Ascites		
Absent	443	87.55
Present	63	12.45

4.5 Distribution of Route of hepatitis B exposure

In assessing the possible route of hepatitis B exposure among the patients, the commonest association was a positive family history as about 12% (83/455) of patients had such history. Six percent (6%) of the patients has had blood transfusion. Less than 0.5% of the patients were injection drug users. Tattooing, scarification and piercing were positive in about 4% of the patients. Table 4 provides details of the hepatitis B exposure routes identified among the patients.

Table 4.4: Distribution of Route of hepatitis B exposure

	No	**Yes**	**Not documented**
	n (%)	**n (%)**	**n(%)**
Family history	372(52.54)	83(11.72)	253(35.73)
Blood transfusion	420(59.32)	43(6.07)	245(34.6)
Tattooing	356(50.28)	8(1.13)	344(48.59)
Scarification	339(47.88)	12(1.69)	357(50.42)
Piercing	327(46.19)	5(0.71)	376(53.11)
Injection drug use	345(48.73)	4(0.56)	359(50.71)

4.6 Clinical features of liver disease

Table 5 shows the clinical features of liver disease presented by the patients. Among all the symptoms presented, jaundice, abdominal pain and loss of weight were the three most occurring symptoms. About one-fifth of the patients presented with jaundice and loss of weight each. The proportion of patients with abdominal symptoms were 29.52% (209/708).

For physical signs, jaundice (15.4%), hepatomegaly (15.8%) and peripheral oedema (12.23%) were the commonest signs identified among the patients (Table 5).

Table 4.5: Clinical features of liver disease

	No	Yes	Not documented
Symptoms	n(%)	n(%)	n(%)
Jaundice	449(63.42)	153(21.61)	106(14.97)
Abdominal pain	379(53.53)	209(29.52)	120(16.95)
Loss of weight	401(56.64)	158(22.32)	149(21.05)
Physical signs			
Jaundice	566(79.94)	109(15.4)	33(4.66)
Peripheral oedema	552(77.97)	87(12.29)	69(9.75)
Hepatomegaly	553(78.11)	112(15.82)	43(6.07)
Splenomegaly	623(87.99)	14(1.98)	71(10.03)

4.7 Results of the Patient's Hepatitis B serology

Of the 692 patients with documented HBeAg status, about 21% (146/692) were HBeAg positive. (Table 6).

Table4.6: Results of the Patients' Hepatitis B serology

	Negative	Positive	Don't know
	n (%)	n(%)	n(%)
HBeAg	488 (70.52)	146 (21.1)	58 (8.38)
HBeAb	146 (21.1)	488 (70.52)	58 (8.38)

4.8 Results of virologic, biochemical response over the one-year period

The distribution of virologic, biochemical and liver disease response to treatment are shown in Table 7. The median level of HBV-DNA prior to treatment was log 4.5(34261.5IU/ml). This decreased to log 2.6 after 6 months of treatment and again reduced over the one-year treatment period to log 1.3 (20IU/ml). Of the 216 patients who started treatment 56% (121/216) of them were able to repeat their viral loads after 6 months and 60% (130 /216) had viral loads done after one year of therapy.

The median level of ALT (mmol/l) also decreased steadily from an average pretreatment level of 50 mmol/l to 32mmol/L after 6 months of therapy and normalized at 25 mmol/l over a one-year treatment period.

Table 4.7: Results of virologic, biochemical response over the one-year period

	Before treatment N (%)	6months after treatment N (%)	1 year after treatment N (%)
HBV DNA (log IU/ml)			
Median (LQ, UQ)	4.5(3.2, 4.9)	2.6(1.3, 3.6)	1.3(1.3,2.0)
<20	10(5.46)	63(52.07)	104(80.0)
>20	204(94.54)	58(47.93)	26(20.0)
ALT (mmol/l)			
Median (LQ, UQ)	50(40, 81)	32(24, 45)	25(20, 33)

Abbreviations: HBV-DNA; hepatitis B viral load, IQR, interquartile rage; ALT, serum alanine amino transferase.

4.9 Distribution of treatment outcomes

The distribution of treatment outcomes is shown in Table 8. The proportion of patients with HBV DNA undetected at one year was about 67.59% of the patients (146/216). More than half of the patients attained normalization of ALT (55.8%, 87/156) and AST (53.5%, 157). HBeAg conversion was attained by only 13.8% among 110 patients with such records.

Table 4.8: Distribution of treatment outcomes

	Frequency	Percentage
HBV DNA undetected		
No	58	26.85
Yes	146	67.59
Missing	15	6.94
ALT		
No	70	44.23
Yes	87	55.77
AST		
No	73	46.5
Yes	84	53.5
HBeAg		
No	95	87.15
Yes	15	13.78

4.10 Association between patient characteristics and undetectable HBV DNA status

Table 9 shows the test of association among the individual characteristics and their treatment outcome. From the tests, age at enrollment, age at diagnosis, and ALT level at baseline were identified to be significantly associated with undetectable HBV DNA ($p<0.05$). Averagely, patients who attained undetectable HBV DNA were enrolled at younger age compared to those who did not attain undetectable HBV DNA. Similarly, those who attained undetectable HBV DNA were diagnosed at a younger age. The median ALT level at baseline was significantly higher among patients who attained undetectable HBV DNA compared to those who did not attain undetectable HBV DNA.

Table 4.9: Association between patient baseline characteristics and undetectable HBV DNA

	Undetectable HBV DNA				
	No	**Yes**	**Total**	**chi-square**	**p-value**
Age at enrollment	36 ± 10.87	28.53 ± 8.16			**<0.001§**
Age at diagnosis	34.74 ± 10.37	28.69 ± 8.85			**0.004§**
Marital Status					
Never in union	35(77.78)	10(22.22)	45	0.9923	0.609
Currently in union	66(81.48)	15(18.52)	81		
Formerly in union	3(100)	0(0)	3		
Sex					
Female	37(86.05)	6(13.95)	43	1.4682	0.226
Male	67(77.01)	20(22.99)	87		
BMI					
Underweight	5(100)	0(0)	5		0.552#
Normal	49(81.67)	11(18.33)	60		
Over weight	36(80)	9(20)	45		
Class1 obesity	14(70)	6(30)	20		
Treatment interrupted					
No	45(80.36)	11(19.64)	56	0.0008	0.978
Yes	58(80.56)	14(19.44)	72		
Alcohol use					
No	85(80.19)	21(19.81)	106		1.000#
Yes	15(78.95)	4(21.05)	19		
Use of Herbal medicine					
No	77(78.57)	21(21.43)	98		1.000#
Yes	6(85.71)	1(14.29)	7		
HBeAg					
Not documented	6(75)	2(25)	8	3.4482	0.178
Negative	24(70.59)	10(29.41)	34		
Positive	74(85.06)	13(14.94)	87		
HBV_DNA					
<2000	3(100)	0(0)	3		0.289#
2000-19,999	10(100)	0(0)	10		
>=20000	88(77.88)	25(22.12)	113		
Baseline ALT	47(37, 61)	69(45, 108)			**0.004ǂ**
Albumin	41(39, 44.2)	42(40, 46.8)			0.469ǂ
Alpha fetoprotein	3.3(1.87, 5.2)	3.2(2.6, 4.1)			0.858ǂ
Jaundice					
No	90(78.95)	24(21.05)	114		0.882#
Yes	8(88.89)	1(11.11)	9		
Not documented	6(85.71)	1(14.29)	7		
Hepatomegaly					
No	96(80)	24(20)	120		1.000#
Yes	4(80)	1(20)	5		
Not documented	4(80)	1(20)	5		

§: p-value obtained from the welch t-test, #: p-value obtained from Fishers' exact test, ǂ: p-value obtained from Mann-Whitney t-test.

4.11 Influence of patients' characteristics on HBV DNA undetected viral load status

The effects of individual characteristics on undetectable HBV DNA after at least 6 months' treatment are presented in Table 10. The adjusted regression model revealed, age at enrollment, and age at diagnosis as the only significant predictors of undetectable HBV DNA status of patients. Age at enrollment was associated with an increased odds of attaining virologic response i.e. undetected HBV-DNA. That is, for every year advancement in age at enrollment the odds of attaining HBV DNA undetected viral load status increases by 41% (AOR: 1.41, 95% CI: 1.1 - 1.81). However, age at diagnosis was rather identified to be negatively related to HBV DNA suppression of patients. For each year advancement in age at diagnosis the odds of having ALT normalization decreases by 23% (AOR: 0.77, 95% CI: 0.61 – 0.97).

Table 4.10: Effects of patients' characteristics on HBV DNA undetected viral load status

	Unadjusted			Adjusted		
	UOR	**95% CI**	**P-value**	**AOR**	**95% CI**	**P-value**
Age						
Age at enrollment	1.06	1.02 - 1.1	0.003	1.41	1.1 - 1.81	**0.007***
Age at diagnosis	1.05	1.01 - 1.09	0.006	0.77	0.61 - 0.97	**0.029***
Marital Status						
Never in union	ref			ref		
Currently in union	1.34	0.63 - 2.85	0.447	0.52	0.15 - 1.84	0.309
Formerly in union	1.00			1.00		
Diabetic						
No	ref			ref		
Yes	1.19	0.14 - 10.24	0.872	0.21	0.01 - 3.6	0.283
Sex						0.105
Female	ref			ref		
Male	0.51	0.21 - 1.24		0.36	0.11 – 1.24	
BMI						
Underweight	ref			ref		
Normal	1.31	0.14 - 12.09	0.605	0.67	0.02 - 20.64	0.100
Over weight	0.83	0.09 - 7.81		0.19	0.01 - 6.36	
Class1 obesity	0.71	0.07 - 7.16		0.16	0 - 6.02	
Treatment interrupted						
No	ref			ref		
Yes	1.05	0.5 - 2.19	0.906	0.94	0.36 - 2.47	0.899
Alcohol use						
No	ref			ref		
Yes	1.13	0.4 - 3.16	0.819	0.70	0.19 - 2.66	0.606
Use of Herbal medicine						
No	ref			ref		
Yes	0.56	0.17 - 1.86	0.346	0.75	0.16 - 3.54	0.712
HBeAg						
Not documented	ref			ref		
Negative	0.71	0.17 - 2.89	0.157	0.51	0.08 - 3.26	0.214
Positive	1.56	0.4 - 6.05		1.31	0.21 - 8.28	
HBV-DNA						
<2000	ref			ref		
2000-19,999	0.50	0.05 - 5.19	0.212	0.35	0.03 - 4.71	0.658
>=20000	0.24	0.03 - 1.83		0.34	0.03 - 3.41	
ALT	1.00	1 – 1.04	0.423	1.00	1 – 1.06	0.381
Jaundice						
No	ref			ref		
Yes	2.22	0.49 - 9.97	0.578	5.18	0.64 - 41.79	0.298
Not documented	0.95	0.2 - 4.62		0.89	0.1 - 8.1	
Hepatomegaly						
No	ref			ref		
Yes	0.65	0.17 - 2.52	0.705	0.31	0.04 - 2.28	0.515
Not documented	1.76	0.22 - 14.45		1.07	0.06 - 20.81	

4.12 Association between patients' characteristics and ALT normalization status

Table 11 shows the test of association among and between the individual characteristics and their treatment outcome. From the tests, age at enrollment, age at diagnosis, sex, baseline ALT and Albumin levels were identified to be significantly associated with ALT normalization ($p<0.05$). Averagely, patients who attained ALT normalization were enrolled at an older age compared to those who did not attain ALT normalization (36.04 ± 10.57 vs 32.28 ± 8.12, $p<0.05$). Similarly, those who attained ALT normalization were diagnosed at an older age compared to those who did not attain ALT normalization (35.35 ± 10.35 vs 31.12 ± 8.15, $p=0.028$). With sex, comparatively female patients had the higher proportion of ALT normalization compared to the males (81.58% vs 61.19, $p=0.031$). The median ALT and Albumin levels at baseline were significantly lower among patients who attained ALT normalization compared to those who did not attain ALT normalization.

Table 4.11: Association between patients' characteristics and ALT normalization status

	ALT normalization				
	No	**Yes**	**Total**	**chi-square**	**p-value**
Age					
Age at enrollment	32.28 ± 8.12	36.04 ± 10.57			**0.049***
Age at diagnosis	31.12 ± 8.15	35.35 ± 10.35			**0.028***
Marital Status					
Never in union	11(36.67)	19(63.33)	30	1.41	0.493
Currently in union	21(29.58)	50(70.42)	71		
Formerly in union	0(0)	2(100)	2		
Sex					
Female	7(18.42)	31(81.58)	38	4.68	**0.031***
Male	26(38.81)	41(61.19)	67		
BMI					
Underweight	0(0)	4(100)	4		0.406
Normal	15(30.61)	34(69.39)	49		
Over weight	10(29.41)	24(70.59)	34		
Class1 obesity	8(44.44)	10(55.56)	18		
Treatment interrupted					
No	14(30.43)	32(69.57)	46	0.03	0.853
Yes	18(32.14)	38(67.86)	56		
Alcohol use					
No	26(31.71)	56(68.29)	82	0.11	0.744
Yes	5(27.78)	13(72.22)	18		
Use of Herbal medicine					
No	21(27.27)	56(72.73)	77		0.147
Yes	3(60)	2(40)	5		
HBeAg					
Not documented	2(28.57)	5(71.43)	7	0.01	0.993
Negative	8(29.63)	19(70.37)	27		
Positive	21(30.43)	48(69.57)	69		
HBV-DNA					
<2000	2(25)	6(75)	8	0.80	0.671
2000-19,999	3(21.43)	11(78.57)	14		
Liver enzymes & protein					
>=20000	25(32.47)	52(67.53)	77		
ALT	56(44, 92)	45(34, 52)			**0.000***
Albumin	43(40, 47)	41(38, 44)			**0.014***
Alpha fetoprotein	3.2(1.87, 4.7)	2.8(1.8, 4.6)			0.422
Symptoms & signs					
Jaundice					
No	27(29.67)	64(70.33)	91		0.205
Yes	4(66.67)	2(33.33)	6		
Not documented	2(25)	6(75)	8		
Hepatomegaly					
No	29(30.21)	67(69.79)	96		0.150
Yes	3(75)	1(25)	4		
Not documented	1(20)	4(80)	5		

4.13 Effects of patients' characteristics on ALT normalization status

Table 12 shows the effects of individual characteristics on patients' ALT normalization status after at least 6 months' treatment. From the adjusted regression model, sex, BMI and jaundice status were identified to be significantly predictive of ALT normalization status of patients ($p<0.05$). With regards to sex of patients, male patients had 70% lower odds of attaining ALT normalization compared to the female patients (AOR: 0.30, 95% CI: 0.11 - 0.79). Patients with jaundice and not documented jaundice status each had 77% reduced odds of attaining ALT normalization compared with patients without jaundice. BMI status of the patients was identified to be associated with five times higher odds of attaining ALT normalization.

Table 4.12: Effects of patients' characteristics on ALT normalization status

	Unadjusted			Adjusted		
	UOR	**95% CI**	**P-value**	**AOR**	**95% CI**	**P-value**
Age at enrollment	1.01	0.98 - 1.04	0.402	0.86	0.73 - 1.02	0.092
Age at diagnosis	1.02	0.99 - 1.05	0.238	1.17	0.98 - 1.39	0.082
Marital Status						
Never in union	ref			ref		
Currently in union	1.17	0.63 - 2.15	0.618	1.23	0.49 - 3.09	0.657
Formerly in union	1.00			1.00		
Diabetes						
No	ref			ref		
Yes	0.62	0.13 - 2.84	0.536	1.35	0.14 - 12.78	0.796
Sex						
Female	ref			ref		
Male	0.53	0.27 - 1.04	0.063	0.30	0.11 - 0.79	**0.015***
BMI						
Underweight	ref			ref		
Normal	2.53	1.13 - 5.7	0.079	5.94	1.91 - 18.48	**0.006***
Over weight	2.10	0.88 - 5.03		5.54	1.64 - 18.75	
Class1 obesity	1.00			1.00		
Treatment interrupted						
No	ref			ref		
Yes	0.87	0.48 - 1.58	0.648	0.89	0.42 - 1.87	0.759
Alcohol use						
No	ref			ref		
Yes	0.93	0.42 - 2.06	0.862	1.20	0.44 - 3.33	0.72
Use of Herbal medicine						
No	ref			ref		
Yes	0.44	0.16 - 1.23	0.117	0.44	0.12 - 1.59	0.211

HBeAg						
Not documented	ref			ref		
Negative	1.52	0.47 - 4.92	0.751	3.33	0.75 - 14.73	0.266
Positive	1.24	0.42 - 3.64		2.03	0.52 - 7.9	
HBV-DNA						
<2000	ref			ref	0 - 0	
2000-19,999	1.52	0.42 - 5.48	0.538	4.57	0.89 - 23.61	0.148
>=20000	0.91	0.33 - 2.52		1.51	0.44 - 5.23	
ALT	1.00	1 - 1	0.673	1.00	1 - 1.03	0.935
Albumin	0.98	0.95 - 1.02	0.362	0.99	0.94 - 1.03	0.6
Alpha fetoprotein	1.00	1 - 1	0.425	1.00	1 - 1.02	0.39
Jaundice						
No	ref			ref		
Yes	0.45	0.19-108	0.128	0.23	0.07 - 0.77	**0.033***
Not documented	0.49	0.14-1.69		0.23	0.03 - 1.76	
Abdominal pain						
No	ref			ref		
Yes	0.86	0.32-2.30	0.952	1.14	0.32 - 4.09	0.969
Not documented	1.02	0.44-2.33		0.91	0.25 - 3.38	
Weight loss						
No	ref			ref		
Yes	1.12	0.52-2.43	0.813	1.18	0.44 - 3.17	0.774
Not documented	0.83	0.39-1.77		1.64	0.4 - 6.76	
Hepatomegaly						
No	ref			ref		
Yes	1.07	0.32-3.62	0.984	2.40	0.5 - 11.44	0.521
Not documented	1.11	0.28-4.45		1.59	0.17 - 15.32	

Serologic Outcomes

The proportion of patients with positive HBeAg status who seroconverted after at least six months of treatment was 13.8%. However, none of the patients lost the HBsAg.

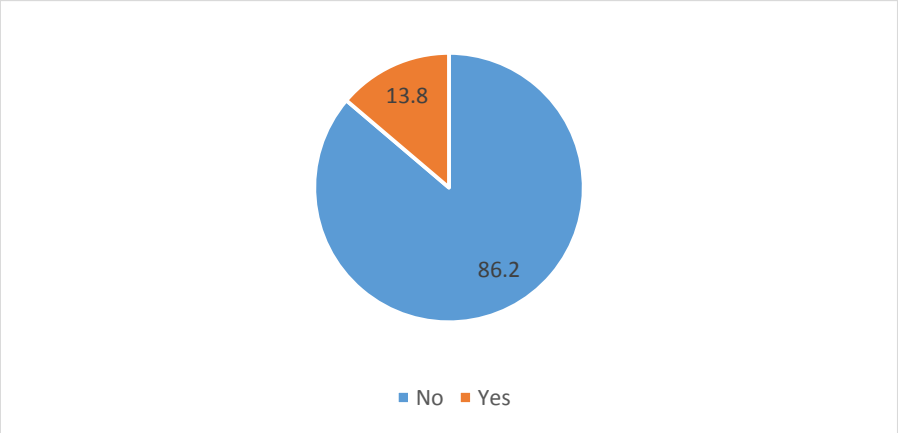

Figure 4: Distribution of HBeAg after treatment among HBeAg positive patients

CHAPTER FIVE

DISCUSSION OF FINDINGS

5.1 Summary

Hepatitis B is a worldwide problem with sub-Saharan Africa being one of the hardest hit. It leads to liver cirrhosis and cancer. Efforts are being made by WHO to eliminate hepatitis B as a public health threat and this includes creating awareness, screening, vaccination and linking those infected to care for management. The World Health Assembly in collaboration with WHO aim at reducing the incidence of viral hepatitis by 90% and mortality by 65% (WHO, 2016). To reduce the risk of transmission and complications, antiviral therapy plays a major role and hence the need to scale up treatment coverage. This study sought to determine factors affecting antiviral treatment outcomes in patients with chronic hepatitis B infection in the era of reduced low cost generic drugs.

5.2 Demographic Characteristics

Averagely, the study participants were found to be young adults of average age 38 years, which is comparable with similar studies done in Canada (Heathcote et al., 2011), Ghana (36 years) (Archampong T N, 2016), Asia (45 years) (Aung et al., 2013) and in Gambian (43 years) (Taylor-Robinson et al., 2016). The high prevalence of HBV in the younger population is a common trend in most sub-Saharan African countries due to high prevalence of HBV. In Africa, HBV is mainly spread from mother to child at birth (vertical transmission) or may be through horizontal transmission thus further explaining the younger age at presentation. There was male predominance (66%) in this study mirroring what has been observed in many studies in Ghana, Ethiopia and Asia (56.6%, 54% and 73% respectively) (Archampong T N, 2016; Aung et al., 2013; Desalegn et al., 2018). This may be because males are six times more at risk of developing chronic hepatitis compared to females (Taylor et al., 2009). Furthermore, men turn to engage in risky life

style resulting in increased risk of acquiring hepatitis B infection. Unhygienic circumcision can also predispose them to the virus. The response to treatment with interferons by males are usually lower compared to females (Lampertico et al., 2017). Furthermore, this may be as a result of delayed clinic attendance or poor compliance on the part of males. The study also showed that most of the patients were married (59%). Unprotected sex is known to cause transmission albeit minimal compared to vertical and horizontal transmission and married people tend to have unprotected sex which could account for the high proportions. This observation was similar to other studies done in Ethiopia where about 62% were married (Desalegn et al., 2018). A systematic review done on pregnant women in Africa also showed a little over half of them were married (Bigna et al., 2019) and the Nigerian national study showed 67.4% (Olayinka et al., 2016).

The significant family history of Hepatitis B in 12% of the patients may be as a result of the vertical or horizontal mode of transmission in this study. Early childhood exposure leads to chronicity in about 95% of cases with persistence of the HBeAg in some of the patients thus remaining a reservoir for the infection. Patients who acquire HBV at an earlier age in addition to the increased chronicity are less likely to lose the HBsAg (Taylor et al., 2009). Complications also turn to occur much frequently in the younger population compared to older age as seen in the western world (Zakharia et al., 2018). Majority of the patients were educated and over a third have had tertiary education. It may be assumed that they have a better knowledge so went to be screened and also were able to afford investigations due to their economic power.

Proportion of patients on treatment

There are various treatment guidelines defining who requires treatment for hepatitis B. Patients with active hepatitis defined as elevated ALT and viral load above 2,000IU/ml in HBeAg-negative

hepatitis and viral load greater than 20,000IU/ml in HBeAg-positive and cirrhotic patients etc. Of the 708 charts reviewed, one third of them were on treatment similar to what Desalegn and co-authors found in their cohort (Desalegn et al., 2018). This is not surprising because the WHO found out that of the over 250 million with hepatitis B globally, only a little over10 % were aware of their hepatitis B status and of these, less than a fifth were on treatment (WHO, 2017). Although 30% in this case appears to be higher than the global estimates, the population were patients who had some form of complication and therefore were referred to a teaching hospital. The low proportion of patients with chronic Hepatitis B infection (CHB) on treatment is alarming. This low proportion of patients on treatment may imply delayed presentation, poor access and limited knowledge on the parts of patients or practitioners. Attaining viral suppression and ALT normalization reduces the risk of developing complications and translates to better clinical outcomes. Some of the patients were unable to do the investigations to help determine if they required treatment or not. This is due to the high cost of investigating and treating the disease. Baseline investigation could cost on the average 800 Ghana cedis ($150) and treatment 200 Ghana cedis ($40) per month which is out of reach for most Ghanaians. In Ghana, the minimum daily wage set by the national tripartite committee 2019 is 10.65 Ghana cedis ($2).

Medication prescribed

As per the WHO treatment and Ghana treatment guidelines, the first choice of antiviral is the nucleos(t)ides. Although there has been a price drop in antiviral medication, it is still beyond reach of the average Ghanaian and there is no policy on treatment regarding hepatitis B in the National Health Insurance Scheme. The two common drugs used over the period were tenofovir (81%) and Lamivudine (18.89%). Those on lamivudine, were later changed to tenofovir. One of the patients was on entecavir that was initiated outside the country and two on pegylated interferon. These

drugs are used because they are available and relatively affordable. They are also effective and are associated with fewer side effects.

5.3. Pre-treatment factors

The seroprevalence of HBeAg in this study was 21.1% similar to other studies done in Africa. Studies done in Ghana and Nigeria have shown a prevalence of HBeAg positive between 8-18% (Akinbami et al., 2012; Archampong T N, 2016; Forbi, Iperepolu, Zungwe, & Agwale, 2012; Rufai,Tanko, Mutocheluh Mohammed, Kwarteng, Kwaku, Dogbe, 2014). This finding is important in the fight against hepatitis B transmission. HBeAg positive patients have very high amount of virus in their blood and serve as a source of infection. These are also people who acquired the infection in their early childhood. This goes to reiterate the importance of the birth dose against hepatitis B in Ghana. Analysis of the patients' data revealed a significant number of patients with HBeAg- negative positive serology. Other studies conducted in Ghana also show a similar pattern (Akinbami et al., 2012; Archampong T N, 2016; Rufai,Tanko, Mutocheluh, Kwarteng, & Dogbe, 2013). HBeAg negative cases are also predominant in Ethiopia (Desalegn et al., 2018) and Nigeria (Akinbami et al., 2012; Forbi et al., 2012). Similar patterns have been observed in Brazil (Gama et al., 2011) Asia (Liaw, 2013) and Canada (Heathcote et al., 2011). Patients with HBeAg-negative have lost their antigen due to mutations and tend to have fluctuating ALT levels sometimes delaying in the initiation of treatment resulting in HBV related complications and poor treatment outcomes.

Body mass index, co infection with hepatitis C, complementary alternative medicine, fatty liver and preexisting liver disease were not predictors of outcomes. This may be as a result of the small numbers with the above. With regards to BMI, most studies done have been silent on it except in

its clinical outcomes in hepatitis C patients. Few studies have associated BMI with increased HBV DNA but not with treatment outcomes.

Twelve percent (12%) of patient had documented use of herbal medication in the past. It will still be advisable to educate patients on the drug-drug interactions between antivirals and herbal medication. Some herbal medications can also be toxic to the liver resulting in liver damage and increased risk of complications. A third of the patients had abdominal pain and 12% had ascites which indicates severe liver impairment.

Treatment outcomes

The ultimate aim of treatment is to eradicate the Hepatitis virus (HBsAg) however this is daunting to say the least due to the incorporation of the covalently closed circular DNA in the liver cells serving as a reservoir for the virus. This has led to the use of undetectable viral load as the endpoint of treatment. Research has revealed that sustained suppression of the virus results in reduced risk of HBV related complications (Younossi et al., 2018). Many studies used HBV-DNA as a surrogate for ultimate treatment response (Aberra et al., 2017; Desalegn et al., 2018; Man-Fung Yuen et al 2015). After a year of treatment, about 68% of the patients attained viral suppression. This is higher compared to 52% by Aung et al (Aung et al., 2013). Desalegn et al however had a better response rate of 85% viral suppression in their cohort (Desalegn et al., 2018). The difference may be that in this study the patients paid for the medication out of pockets and may not have been fully compliant whilst those in the Ethiopian study, were provided with the medicines. Heathcote and co-authors also in their study observed a response rate of 87% after 144 weeks of tenofovir therapy (Heathcote et al., 2011). Another reason for the difference in the HBV- DNA outcomes may be due to the duration of therapy which is shorter compared to that by Heathcote. Better

clinical outcomes are achieved if there is concomitant ALT normalization. Almost two thirds of the overall patient achieved ALT normalization after one year of treatment. Inflammation of the liver is characterized by elevated serum ALT levels. Persistence of the ALT will lead to cirrhosis and liver cancer. Although it does not reflect viral replication, HBV DNA suppression leads to concomitant normalization of the ALT. Patients with marginally elevated ALT achieved HBV DNA suppression and loss of HBeAg-positive compared with those with high levels in this study however this was not statistically significant. Therefore, a composite outcome with HBV DNA suppression and ALT normalization will lead to a better clinical outcome. In this study, there was no HBsAg loss after one year of treatment. This goes to buttress the difficulty in achieving HBsAg loss.

Factors predicting hepatitis B outcomes

Predictive factors for treatment outcomes in this study was age at diagnosis and enrollment, sex, jaundice and pretreatment ALT. These were significantly associated with both HBV DNA suppression and ALT normalization. Various studies have shown that baseline viral load, ALT levels and HBeAg status predict treatment outcomes (Aung et al., 2013; Desalegn et al., 2018; Heathcote et al., 2011) however in this study, baseline viral load and HBeAg status did not predict virologic response. Effect of alcohol on treatment outcomes has not been documented in CHB patients. Interestingly being an alcohol user did not in any way predict treatment outcomes. Although theoretically alcohol is supposed to reduce the defense system of the patient and increase liver injury, it may be that most of them stopped after knowing their diagnosis. Wang et al found in their cohort a higher risk of liver cirrhosis and liver cancer in CHB with significant alcohol intake who were not on treatment. Chih-Wen et al reported no significant effect of hazardous alcohol use on hepatitis B treatment outcomes (Chih-Wen et al., 2017). BMI was predictive of

biochemical outcomes but not on HBV-DNA unlike its effect on treatment outcomes in patients with chronic hepatitis C (Chen et al., 2018; Chiang et al., 2012). Fatty liver is known to decrease response rate to interferon treatment in chronic hepatitis C patients, but this is not documented for hepatitis B.

CHAPTER SIX

6.1 Conclusion

The study highlights the low proportion of patients with chronic Hepatitis B infection (CHB) on treatment; even though two-thirds of the patients attained viral suppression after one year of treatment. Viral suppression reduces the risk of developing complications and translates to better clinical outcomes. This low proportion of patients on treatment may imply delayed presentation, poor access, and limited knowledge on the parts of patients or practitioners. Attaining viral suppression and ALT normalization are an important treatment outcomes.

This study also highlights predictive factors for treatment outcomes in Ghana where nucleos(t)ide were the primary drugs used. The predictors of positive treatment outcomes were age at presentation and age at diagnosis, sex, baseline ALT and clinical disease (Jaundice). Timely diagnosis and treatment before jaundice develops may also improve treatment outcomes.

A fifth of the patients demonstrated seropositivity to Hepatitis B envelope antigen (HBeAg) which often correlates with high viral loads and serve as reservoirs of infection. As they are more likely to acquire infection by vertical transmission, this makes a strong case for prevention of transmission from mother to child and vaccination of the infant with a birth dose. This is critical to the immunization schedule for under-five children. Counterintuitively, the high levels of HBeAg negative patients, who may have fluctuating levels of biochemical parameters may have delayed presentation resulting in complications. This may have implications for periodic screening especially among persons at risk and of young age.

6.2 Recommendation

1. The prevalence of HBeAg-positive was high and therefore there is a need to include HBV birth dose in our national expanded programme on immunization.
2. The options and strategy to improve financial access i.e. subsidizing; enrolling in access programs for cheaper medicines should be looked at by policy makers.
3. Government to expand the national health insurance scheme to include treatment of hepatitis B to help improve access to the drugs and address issues with treatment disruptions.
4. Periodic screening for hepatitis B especially among persons at risk and of young age is strongly recommended.
5. Education of the population about the hepatitis B disease epidemiology and availability of treatment will help to improve care seeking behavior and early access to treatment.
6. Integration of hepatitis B treatment into existing national programmes such as the HIV or malaria programme to improve early access to hepatitis B care.

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Appendix A Data Abstraction Tool

Factors influencing treatment outcomes of chronic hepatitis B in patients attending the Korle Bu Teaching Hospital.

Project summary: The purpose of this study is to gather demographic, serologic and treatment information on patients with hepatitis B virus infection through medical records.

Eligibility criteria

Patients aged between 14years and 70years who have been confirmed to have HBV infection with documentary evidence on treatment for at least six months.

Dr. Adwoa Agyei-Nkansah
University of Ghana School of Public Health
Tel: 0208123076
Email: afrakomaagyei@gmail.com

1. Socio Demographic features

Date:_ __/__ __/__ __

Patient Initial ……. Study ID number: ……..

Hospital number: …… Contact number: ……..

Date of birth/age…….. Sex: □ male □ female

Occupation: ……., Level of education: □ none □1° □2° □ 3°

Area of residence: ……

Marital status □ single □ married □ divorced □ separated □ cohabiting □ widowed

Ethnicity: □ Ga □Akan □ Ewe □ Hausa □ Dagbani □ Nzema □ Non Ghanaian

Weight: …… (Kg) Date of enrolment: ……

Height: ……(m) BMI:

2. HBV medical history

HBs Antigen □ Positive □ Negative

Date of HBV diagnosis: __ __/__ __/__ __ __ __

(DD/MM/YYYY)

3. Exposure characteristics

Route of exposure	**Please tick appropriate box below**		
	YES	**NO**	**NOT DOCUMENTED**
Family history of hepatitis B			
Blood transfusion			
Tattooing			
Piercing			
Scarifications			
IV drug use			
Multiple Sexual partners			
Not documented			

4. Co-Morbid conditions:

4.1. HCV **antibody status**: □ Positive □ Negative

4.2. Diabetes **mellitus**: □ yes □No

If yes, duration of disease: □<6months □ 6-12months □ 1-5yr □ >5yr

4.3.**Fatty liver**: □ yes □No

4.5 **History of liver Disease**: □ yes □No

4.6 Alcohol use □ yes □No

If yes

Type of alcohol: □Beer □Wine □ Whisky □Brandy

Number of units (per week): □<14 □ >14

Duration of alcohol use? □<6months □ 6-12months □ >1yr

4.7 Use of herbal medicines □ yes □No

How long has patient been using herbal medications: ……months

5. Clinical features of liver disease

Symptoms	**Please tick appropriate box below**		
	YES	**NO**	**NOT DOCUMENTED**
Asymptomatic			
Jaundice			
Pedal oedema			
Abdominal distension			
Others: please specify			
Physical signs	**Please tick appropriate box**		
	YES	**NO**	**NOT DOCUMENTED**
Jaundice			
Ascites			
Hepatomegaly			
Splenomegaly			
Others: please specify			

6. What are the results of the patient's Hepatitis B serology

Please tick the appropriate response below:

	Positive	**Negative**	**Don't know**
HBeAg			
HBeAb			
Hepatitis C serology			

7. What are the results of the patients viral titres and liver biochemistry test

Please indicate below the following serological values

	Viral Serological Titres			
Dates				
HBV DNA(IU/ml)				
Liver Biochemistry Test				

Dates(D/M/YYYY)				
Total bil (mmol/l)				
Direct bil(mmol/l)				
AST(mmol/l)				
ALT(mmol/l)				
ALP(iu/l)				
GGT(iu/l)				
Albumin(g/l)				
Alpha fetoprotein				

8. Other liver investigations

Abdominal Ultrasound scan	***Tick where appropriate:*** **Liver:** Normal ☐ yes ☐ no Enlarged ☐ yes ☐ no **Spleen**: Normal ☐ yes ☐ no Enlarged: ☐ yes ☐ no **Ascites**: ☐ present ☐ Absent
Liver histology	Fibrosis ☐ yes ☐ no Fatty liver ☐ yes ☐ no

9. Anti-viral therapy

Is patient on medication for hepatitis B? ☐ Yes ☐No

If yes when was treatment started? __ __/__ __/__ __ __ __

(DD/MM/YYYY)

Antiviral regimen: …….

Drug	Tick as appropriate	Date initiated	Duration on treatment in months	
			6	12
Lamivudine				

Pegylated interferon				
Tenofovir				
Entecavir				
Herbal				

10. Adherence

Was treatment interrupted? □ Yes □ No

If yes why? (Please tick):

Treatment interruptions	Yes	No	Comments (state)
Poor compliance			
Side effects			
Non availability			
Poor response			

11. Treatment outcomes

Tick where appropriate

Serological outcomes		
Parameter	**Yes**	**No**
HBsAg seroconversion		
HBeAg seroconversion		
Biochemical outcomes		
ALT normalization		
Virologic outcomes		
Undetectable HBV DNA		
Histological outcomes		
Normalisation of liver histology		

Appendix 2⁎ Antiviral agents' active against hepatitis B virus infection

Antiviral	**Resistant barrier**	**HBeAg seroconversion (%)**	**HBV DNA suppression (%)**	**HBsAg loss (%)**	**ALT levels (IU/ml)**
Pegylated Interferons	Not Applicable	29-32	7-14	3-7	32-41
Tenofovir	High	21	76	3	68
Entecavir	High	21	67	2	68
Lamivudine	low	16-18%	36-44	0-7	41-72
Adefovir	Moderate	12-18	13-21	0	48-54

⁎ WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection March 2015.

APPENDIX: 3 Ethical Clearance

In case of reply the number
And the date of this
Letter should be quoted
My Ref. No: KBTH/IMS/03/19
Your Ref. No.....

KORLE BU TEACHING HOSPITAL
P. O. BOX KB 77,
KORLE BU, ACCRA.

Tel: +233 302 667759/673034-6
Fax: +233 302 667759
Email: Info@kbth.gov.gh
pr@kbth.gov.gh
Website: www.kbth.gov.gh

19th February, 2019

DR. ADWOA AGYEI-NKANSAH
DEPT. OF MEDICINE
KORLE BU

FACTORS INFLUENCING TREATMENT OUTCOMES OF CHRONIC HEPATITIS B IN PATIENTS ATTENDING THE KORLE BU TEACHING HOSPITAL

KBTH-IRB /000138/2018

Investigator: Dr. Adwoa Agyei-Nkansah

The Korle Bu Teaching Hospital Institutional Review Board (KBTH IRB) reviewed and granted approval to the study entitled "Factors influencing treatment outcomes of chronic hepatitis B in patients attending the Korle Bu Teaching Hospital"

Please note that the Board requires you to submit a final review report on completion of this study to the KBTH-IRB.

Kindly, note that, any modification/amendment to the approved study protocol without approval from KBTH-IRB renders this certificate invalid.

Please report all serious adverse events related to this study to KBTH-IRB within seven days verbally and fourteen days in writing.

This IRB approval is valid till 30th December, 2019. You are to submit annual report for continuing review.

Sincere regards,

MR OKYERE BOATENG
CHAIR (KBTH-IRB)

Cc: The Chief Executive Officer
Korle Bu Teaching Hospital

In case of reply the number
And the date of this
Letter should be quoted
My Ref. No KBTH/IM&S/C3/19
Your Ref. No.....

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19th February, 2019

DR. ADWOA AGYEI-NKANSAH
DEPT. OF MEDICINE
KORLE BU

INSTITUTIONAL APPROVAL: KORLE BU TEACHING HOSPITAL-SCIENTIFIC AND TECHNICAL COMMITTEE/INSTITUTIONAL REVIEW BOARD (KBTH-STC/IRB/000138/2018

Following approval of your study entitled "Factors influencing treatment outcomes of chronic hepatitis B in patients attending the Korle Bu Teaching Hospital" by the Korle Bu Teaching Hospital-Scientific and Technical Committee/Institutional Review Board.

I am pleased to inform you that institutional approval has been granted for the conduct of your study in Korle Bu Teaching Hospital.

Please contact the Head of Department to discuss the commencement date of the study.

Please note that, this institutional approval is rendered invalid if the terms of the Institutional Reviewed Board/Scientific and Technical Committee approval are violated.

Sincere regards,

Dr. Samuel Asiamah
Director of Medical Affairs
For: Chief Executive Officer

Cc: The Chief Executive
Korle Bu