A TWO-YEAR RETROSPECTIVE STUDY ON HEPATITIS B CASES IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM) FROM 2018 – 2019

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by

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DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated and duly acknowledged.

I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at Universiti Sains Malaysia or other institutions.

I grant Universiti Sains Malaysia the right to use the dissertation for teaching, research and promotional purposes.

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Chong Yuen Sang
Master of Science (Biomedicine) Mixed Mode

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LIST OF ABBREVATION

AST	Alanine aminotransferase
AVT	Antiviral therapy
CDC	Center for Disease Control and Prevention
CHB	Chronic Hepatitis B
cccDNA	Covalently closed circular DNA
DNA	Deoxyribonucleic acid
dsDNA	Double stranded Deoxyribonucleic acid
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HCC	Hepatocellular Carcinoma
HUSM	Hospital Universiti Sains Malaysia
HV	Hepatitis Virus
IFN	Interferons
JEPeM	Human Research Ethics Committee
LHBs	Large envelope protein
MOH	Ministry of Health
MNCR	Malaysia National Cancer Registry

NSPHBC	National Strategic Plan of Hepatitis B and C
NA	Nucleosides analogues
WHO	World Health Organization

KAJIAN RETROSPEKTIF SEPANJANG DUA TAHUN BAGI KES HEPATITIS B DI HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM) DARI 2018 – 2019

ABSTRAK

Jangkitan virus Hepatitis B (HBV) adalah penyakit berjangkit yang amat serius di seluruh dunia. Jangkitan HBV sangat tinggi di kawasan endemik yang merangkumi Asia Tenggara (SEA) dan Malaysia adalah antara negara yang mempunyai insiden jangkitan hepatitis B (HB) yang paling tinggi. Memandangkan terdapat kekurangan maklumat mengenai epidemiologi dan data klinikal pesakit, maka tujuan projek ini adalah untuk menganalisa kes HB yang dilaporkan di Hospital USM, Kubang Kerian, Kelantan. Walaupun data dikumpulkan dari satu hospital, kawasan tadahan hospital ini besar kerana kebanyakan pesakit dari negeri Kelantan dirujuk atau masuk ke hospital ini untuk diagnosis dan rawatan. Data diekstrak dari sistem informasi hospital dan dieksport ke Microsoft excel dan dianalisa menggunakan perisian SPSS versi 26.

Terdapat 232 pesakit HB yang baru didiagnosis dan sedang menjalani pemeriksaan di Hospital USM dari 2018 hingga 2019 yang menjadi subjek kajian penyelidikan ini. Dari jumlah itu, 65% pesakit HB adalah lelaki dan kebanyakan pesakit berada dalam kumpulan usia yang produktif secara ekonomi antara 30 hingga 60 tahun. Mengenai etnik, kebanyakan pesakit adalah orang Melayu dan diikuti oleh orang Cina dan India. Selain itu, majoriti pesakit HB adalah bukan kumpulan pekerja kesihatan dan kumpulan yang telah bersara. Data klinikal HB menunjukkan lebih banyak pesakit dijangkiti HB secara kronik daripada akut. Rawatan biasa yang diberikan kepada pesakit HB kronik adalah ubat antivirus (AVT) dan interferon (IFN). Kedua-duanya

adalah standard rawatan perawatan untuk jangkitan kronik HB. Walaupun begitu, analisis univariat dimasukkan dalam kajian penyelidikan ini. Dari analisis, kami berjaya mengkaji hubungan antara umur dan taburan sosio-demografi lain hanya untuk jantina pesakit HB, fasa jangkitan dan komplikasi jangkitan HB. Faktor risiko jangkitan HB yang termasuk dalam kajian ini adalah umur, jantina dan etnik. Hasil kajian menunjukkan bahawa, tidak ada signifikan secara statistik dalam hubungan faktor risiko ini.

Memandangkan data yang diperoleh dalam kajian ini adalah data sekunder, beberapa data tidak tersedia dan mungkin tidak dikemas kini dari semasa ke semasa. Oleh itu, tidak cukup komprehensif untuk menggambarkan prevalens kes HB di Malaysia. Kajian yang sedang berjalan sangat penting untuk mengatasi keterbatasan dalam projek ini dan menetapkan data epidemiologi jangkitan HB akan menjadi penting untuk maklumat kesihatan awam.

A TWO-YEAR RETROSPECTIVE STUDY ON HEPATITIS B CASES IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM) FROM 2018 – 2019

ABSTRACT

Hepatitis B virus (HBV) infection is a deadly infectious disease worldwide. HBV infection is predominantly high in endemic region which includes Southeast Asia (SEA). Malaysia is one of the endemic country in SEA and has higher incidences of hepatitis B (HB) infection. Given that, there is a paucity of information on epidemiological trend and patient clinical data, therefore the goal of this project is to analyze HB cases reported to Hospital USM, Kubang Kerian, Kelantan. Although data was collected from a single hospital, the catchment area of this hospital is large as most patients from Kelantan state are referred or walk in into this hospital for diagnosis and treatment. Data were extracted from the hospital information system and exported into Microsoft excel and were analysed using SPSS software version 26.

There are total 232 HB patients are newly diagnosed and on-going follow up in Hospital USM from 2018 until 2019 were the subjects of this research study. Of that, 65% of HB patients were males and most patients were in the economically productive age group between 30 to 60 years old. Regarding ethnicity, most of the patients are Malays followed by Chinese and Indians. Besides that, majority of the HB patients were non-healthcare workers and retired group. The clinical data of HB indicated more patients were chronically infected with HB than acute. The common treatment that were administered to chronic HB patients are antiviral drugs (AVT) and interferons (IFN). Both are standard of care treatment for chronic hepatitis B (CHB) infection. Nevertheless, the univariate analyses were included in this research study. From the

analyses, we manage to establish an association between age and other socio-demographics distributions only for HB patient gender, phase of infection and complication of HB infection. The risk factors of HB infection included in this study were age, gender and ethnicity. The results shown that, there is not statistically significance in these risk factors.

Given the data obtained in this study were secondary data, some of the data are not available and might not be updated from time to time. Thus, it is not comprehensive enough to reflect the prevalence of hepatitis B cases in Malaysia. On-going study is crucial to overcome the limitation in this project and establish of the epidemiological data of hepatitis B infection would be important for public health information.

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

1.1 Background of the study

Hepatitis B (HB) has become an important viral disease infecting human worldwide and is one of major public health concern in the world. Hepatitis B infection is caused by Hepatitis B virus (HBV) which is a DNA virus that mainly infect and replicate in hepatocytes (Valaydon & Locarnini, 2017). Hepatitis B infection can cause both acute and chronic infection. Acute infection is when hepatitis B patients can recover from the infection within six months. However, if the patients are unable to fight the infection within six months it will progress into chronic infection (Yin & Tong, 2006). As one of the hepatotropic virus, HBV can induce necroinflammatory, fibrotic and carcinogenic effects to the liver due to chronic HBV infection (Mak *et al*., 2019). Besides that, chronic HBV infection has greater risk to develop liver cirrhosis and hepatocellular carcinoma (HCC) (Tong & Revill, 2016). The risk of chronic infection depends on the age of the patient, where 90% of the infant and about 25%-50% of children aged between 1-5 years old will have higher chance of progressing into chronic phase (CDC, 2020). Surprisingly, most adults (95%) are able to recover completely from HBV infection. Although, hepatitis B (HB) is a vaccine preventable disease but it has been categorized as a serious infectious disease in the world due to the high prevalence of infection (WHO, 2019).

Transmission of HBV is through blood transfusion, perinatal transmission, sexual contact, exposure to infected blood or body fluids, drugs users and occupational exposure (Rajamoorthy *et al.*, 2016). In highly endemic regions, HBV infection is

mostly transmitted from mother to child. The clinical presentation of HBV infection ranged from asymptomatic (70%), symptomatic (30%) and to fulminant hepatitis with liver failure (Figure 1.1) (Yin & Tong, 2006). However, early detection of HB infection is often a challenge due to the trivial clinical presentation where patient is unaware of the infection. Hepatitis B virus is non-curable by antiviral drugs, but most patients are able to recover from the infection due to their strong immune response.

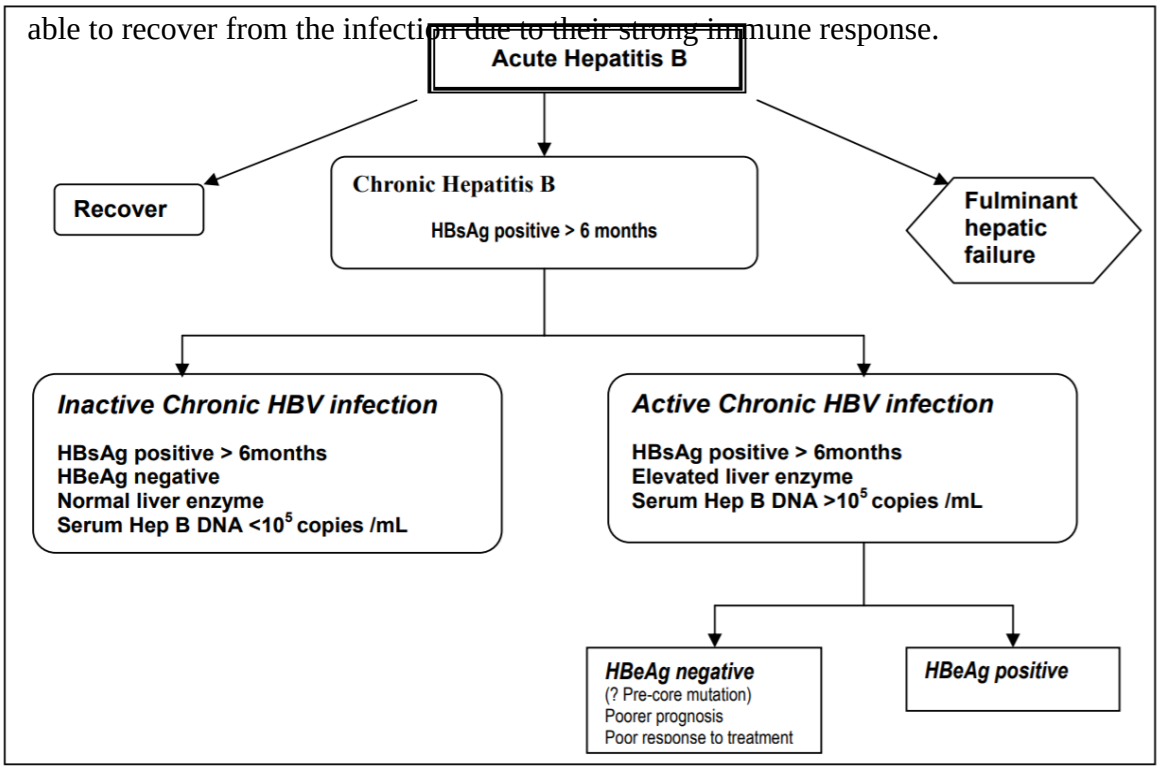

Figure 1.1: Clinical presentation of hepatitis B infection (Source: Yin & Tong, 2006).

Recently, HBV infections are increasing in Malaysia. An estimated 35,861 cases of hepatitis B infection have been reported to the Ministry of Health Malaysia up to year 2017 (MOH Health Facts 2010 & 2016). To date, data regarding the prevalence, distributions and determinants (risk factors) of HBV infection in Malaysia are fragmented and not well documented due to lack of epidemiological study and lesser

emphasis given to this viral disease. The importance of identification and management of HB infection as well as effective implementation of the screening programs may reduce the incidence of HB infection and improve the survival outcomes in HB patients. However, there is a paucity of information in the pattern of prevalence, presentation, clinical outcomes and treatment of HB patients in Malaysia. Several studies on HB infection cases have been reported in Malaysia, but there are no recent updated socio-demographics distribution, prevalence and risk factors as well as treatment data for HB cases particularly in Kelantan (Raihan, 2016). Therefore, investigating the prevalence and risk factors associated with HB infections among the population in Kelantan is pertinent in providing an epidemiological picture of the disease.

Thus, the aim of this study is to determine the prevalence and the risk factors of HB among the patients from the Hospital Universiti Sains Malaysia (HUSM) in Kubang Kerian, Kelantan. Although the data will be collected from a single-site, HUSM receives HB patients not only from Kota Bharu but also from other districts in Kelantan. All data on HB patients from 2018 – 2019 at HUSM will be retrieved from the hospital information system and the medical record unit. Data captured from the hospital information system and the patient medical record, will be imported into Microsoft excel and analysed using SPSS version 26 software.

The research findings will be of importance to the physicians, researchers and community. Most importantly, the study outcome will be helpful to physicians and to public health management in monitoring and controlling the disease thus reducing the risk of transmission and risk of acquired HB infection.

1.2 Overview of Hepatitis Virus

Viral hepatitis is the inflammation of the liver caused by viral causative agents including hepatitis viruses A, B, C, D, E, and G (Ryu, 2016). The most common etiological agents of hepatitis in Malaysia are hepatitis A, B and C viruses (Raihan, 2016). However, clinically significant hepatotropic viruses (A-E) can produce virtually indistinguishable clinical syndromes. Common syndromes associated with viral hepatitis are nonspecific symptoms including fever, nausea, fatigue, arthralgias, myalgias, headache, and sometimes pharyngitis. This is followed by onset of visible jaundice, enlargement of liver, and dark urine caused by bilirubinuria (Cobo, 2014). The clinical course, outcomes, and complications varies with the type of virus causing the hepatitis.

1.2.1 Characteristics of HBV

HBV is one of the smallest enveloped, partially dsDNA virus that belongs to the member of hepadnaviridae family. It consists of an envelope, a core, and a DNA genome, as well as a viral polymerase protein (Figure 1.2) (Bell & Kramvis, 2016). The inner core of the virus consists of hepatitis core antigen (HBcAg), hepatitis B “e” antigen (HBeAg), a circular form of partially double stranded DNA with about 3200 base pairs nucleotides in length and 42nm in diameter (Lok & Kaplan, 2007). Besides that, the envelope is made up of lipids and three different types of surface glycoprotein as shown in Figure 1.2. The characteristics and course of HBV infection is shown in Table 1.1 (Jules & Andrew, 2015).

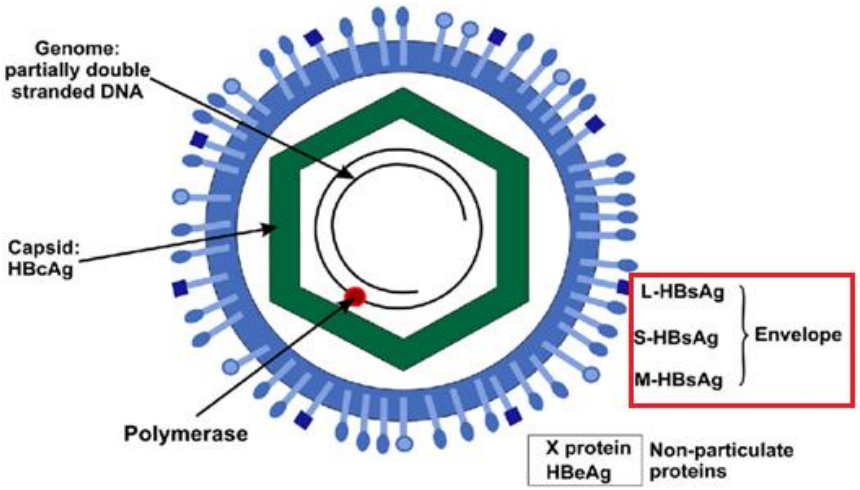

Figure 1.2: Structure of the Hepatitis B virus. (Source: Bell & Kramvis, 2016) HBV consists of envelope protein with three different types of surface glycoprotein (small S, medium M, and large L).

Table 1.1: Hepatitis B virus and their characteristics

Characteristics	**Hepatitis B**
Virus family	Hepadnaviridae
Genus	Orthohepadnavirus
Nucleic acid	DNA
Incubation period (days)	30 – 180 (average 60 to 90)
Mode of transmission	Blood and sexual
Chronic infection	Yes
Cirrhosis and hepatocellular carcinoma	Yes

Source: Jules & Andrew (2014).

Hepatitis B virus (HBV) infection establishes in the liver cells (hepatocytes) as HBV enters liver through the bloodstream and the replication take place in the hepatocytes (Shepard *et al.*, 2006). Early diagnosis and detection of HBV infection is challenging due to the subclinical or asymptomatic infection, nonspecific signs and symptoms in patients (Raihan, 2016). However, the clinical signs and symptoms for acute infection ranged from mild illness to a serious condition which require hospitalization (Raihan, 2016). Patients with HBV infection can be associated with one or more clinical symptoms namely jaundice, abdominal pain, vomiting, fever, dark urine, nausea and hepatomegaly (Shepard *et al*., 2006). Besides that, patients infected with HBV may also progress into chronic infection, which can lead to liver cirrhosis or hepatocellular carcinoma (HCC) (Shepard *et al*., 2006). Unfortunately, HBV diagnosis is cumbersome due to asymptomatic and trivial early clinical symptoms which most patients are unaware of the infection and resulting in a much later detection with manifestations of cirrhosis or HCC.

1.2.2 Hepatitis B Disease Transmission

There are two major routes of transmission that contribute to hepatitis B infection namely vertical and horizontal transmission (WHO, 2019). Vertical transmission is one of the common transmissions of HBV which is perinatal transmission during childbirth as well as from family members to the child (Shepard *et al*., 2006). Horizontal transmission is another route that contributed to HBV transmission especially amongst adult at high risk groups through blood transfusion from infected patients, exposure to infected blood, body fluids, unsafe drugs injection, HIV positive persons and sexual intercourse (Raihan *et al*, 2017). Besides, HBV is able to survive on an inanimate surface up to seven days thus direct transmission from

contaminated surface have been reported as an HBV mode of transmission (Pourkarim *et al*., 2014).

Hepatitis B virus mainly infects hepatocytes, but the mechanism and hallmark of this viral replication is different compared to other viral hepatitis as it replicates by reverse transcription of RNA intermediate and the pre-genomes (Al-Sadeq *et al* 2019). The strategies of HBV infection and replication in the host cells (liver cells) is shown in Figure 1.3.

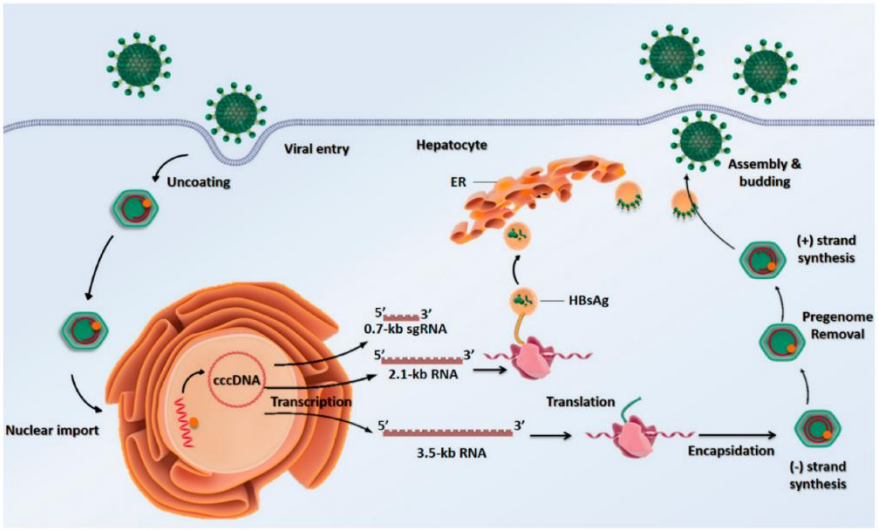

Figure 1.3: Schematic representation of the HBV replication (Source: Al-Sadeq *et al*., 2019).

HBV attaches to the host hepatocyte cell membrane through its envelope proteins. When the viral membrane fuses with the cell membrane, it will result in releasing the viral genome into the cell cytoplasm. After the viral genome reaches the nucleus, the viral polymerase enzyme will convert the partially double-stranded DNA genome into cccDNA. This is followed by transcription and nuclear export of all viral mRNA to the cytoplasm for translation. The surface protein enveloping process occurs in the endoplasmic reticulum and then assembled in the cytoplasm. These proteins are transported to the post-endoplasmic reticulum and Golgi compartments for the budding of the nucleocapsid. The different viral components will assemble into new virions that will be released out of the host and infect new hepatocyte.

1.3 HBV Disease Burden

The following sections elaborate on the incidences and mortality rates of global viral HB infection, current trends of HB infection in Malaysia and Malaysian National Cancer Registry report 2016 for HCC cases.

1.3.1 Global distribution of HBV

World Health Organization (WHO, 2019) reported that two billion individuals have been infected with Hepatitis B virus (HBV) and 360 million are living with chronic infection. Viral hepatitis is a major leading cause of death worldwide since 1990 with 1.46 million deaths, higher than HIV, tuberculosis and Malaria (WHO, 2019). Among all viral hepatitis cases, 90% is due to HBV and HCV infection. Besides, there are 600,000 individuals with HBV infection who die each year due to liver cirrhosis or HCC (El-Serag, 2012). Hepatitis B is the most prevalence and infectious type of viral disease that affect many populations in the world. The mortality rate for HB infection is about 887,000 due to two major liver complication such as cirrhosis and HCC (Liaw & Chu, 2009). As reported by World Health Organization (WHO, 2016), the mortality rates of patients infected with HBV is two times greater than HAV, HCV and HEV (Figure 1.4). The percentage of chronic HBV causing liver cirrhosis and HCC are also higher than chronic HCV infection (WHO, 2019). Globally, the prevalence of positive HB surface antigen (HBsAg) was 3.61% and it is highest in the African region (Schweitzer, *et al*., 2015). In Southeast Asia, an estimated 2.0% of the general population are infected with HBV (Schweitzer, *et al*., 2015).

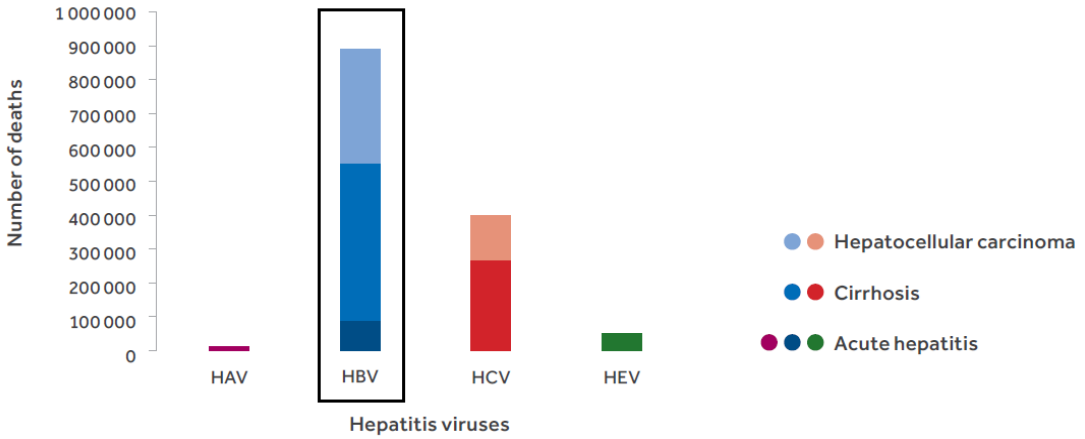

Figure 1.4: Mortality rates of global viral hepatitis infection in 2015 (Source: World Health Organization, WHO, 2016). HBV mortality rates stand two times higher than other viral hepatitis cases (refer to box)

Recent updated global epidemiology of viral hepatitis in 2018 revealed that hepatitis B remained as one of the most common and critical infectious diseases worldwide that leads to significant health complication and mortality (Jefferies *et al.*, 2018). About one-third of the world's population have been infected with HBV. Of that number, around 5% are chronic carriers and a quarter of these carriers develops serious liver diseases such as chronic hepatitis, cirrhosis and HCC (WHO, 2019). Annually, there were 78,0000 HBV-related deaths are documented around the world. However, the risk of progressing chronic infection and liver complications depend on the age of patients. The risk of developing chronic infection due to the infection occuring prenatally is 90%. For instance, sub-Saharan Africa and East Asian countries HBV mainly transmitted through vertical and horizontal route. Surprisingly, in developed countries most of the HBV infections occur by horizontal route in young adults through social factors such as injecting drug or high-risk sexual behavior (Jefferies *et al*., 2018). Besides, seroprevalence (HBsAg) of hepatitis B can be classified into high (>8%),

intermediate (2 – 7%) and low prevalence (<2%) (MacLachlan & Cowie, 2015). Figure 1.5 below shows global distribution of HBV infection.

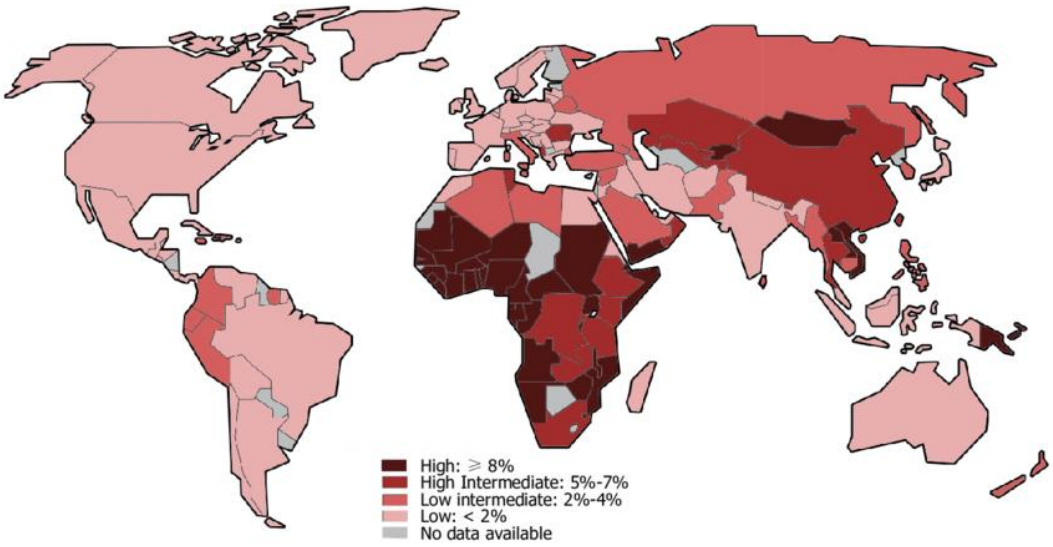

Figure 1.5: Global distribution of hepatitis B infection (Source: Jefferies et al., 2018).

1.3.2 Current Trends of HBV infection in Malaysia

In Malaysia, there are approximately 1 million people infected with chronic hepatitis B (CHB) infection. The incidence rate of people who are infected with hepatitis B is higher than hepatitis A and C. Besides, about 75% of all viral hepatitis cases are due to hepatitis B infection, and the ratio of infection between male-to-female ratios is 2:1. (Raihan, 2016). Chronic hepatitis B stands for more than 80% of the HCC cases seen in Malaysia, and HCC has reported in the top ten most common cancer according to the report from National Cancer Registry in 2016 (Raihan, 2016). Data from the Malaysian Ministry of Health showed the number of deaths due to Hepatitis B is greater than any other vaccine-preventable disease in Malaysia (MOH, 2014). According to the Ministry of Health Malaysia, 5% of Malaysian are infected with HBV

and 80% of the HB patients are between 25 to 55 years old. The prevalence of HBV infection in Malaysia is highest among the Chinese (36%), followed by Malays (26%) and Indians (15%) respectively (Raihan, 2016).

Recently, Ministry of Health Malaysia has reported 35,861 notified cases of viral hepatitis B up to year 2017. The incidence rate of hepatitis B was reported to have increased from 2.26 per 100,000 in 2010 to 12.65 per 100,000 populations in 2015 (MOH Health Facts 2010 & 2016). Figure 1.6 shows, a steady decrease in notifiable cases from year 1990 to 1997 due to the implementation of universal vaccination of infants, which started in 1989. However, there is a sharp increase in reported cases was noted in year 1998 due to the inclusion of mandatory testing of all foreign workers who had arrived in Malaysia (Figure 1.6). In 2000, the incidences of HBV infection showed decrease trend from 2000 until 2009 but in the year 2010, HBV increases again as notification of both acute and chronic hepatitis B infection (Raihan, 2016).

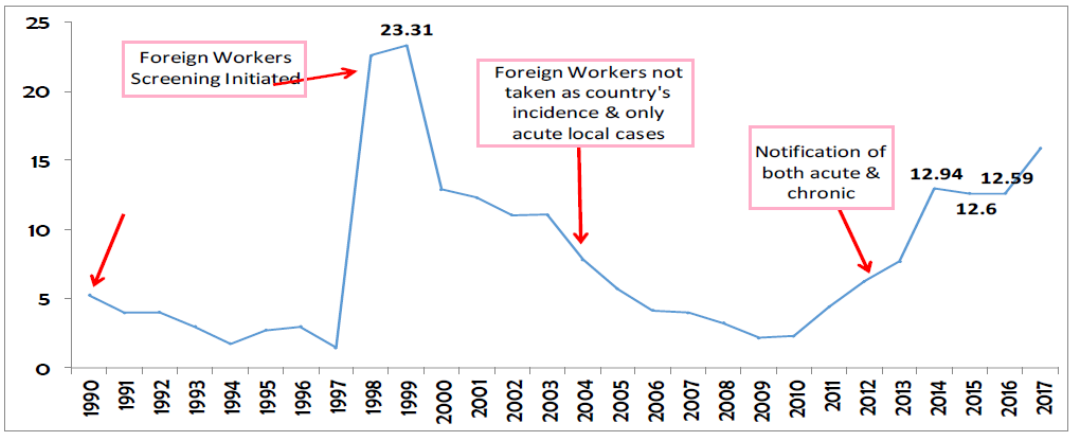

Figure 1.6: Notification rate (per 100,000 population) of hepatitis B in Malaysia from year 1990 – 2017 (Source: Ministry of Health, Malaysia, 2019). The infection rate was reduced after HB vaccination program implemented in Malaysia, 1989.

Malaysia is one of the multi-ethnic countries comprising of 14 states including Sabah and Sarawak. Sabah has the highest incidences of hepatitis B infection followed by Pahang and Johor in Malaysia between 2003 until 2012 as shown in Figure 1.7 (Raihan, 2016).

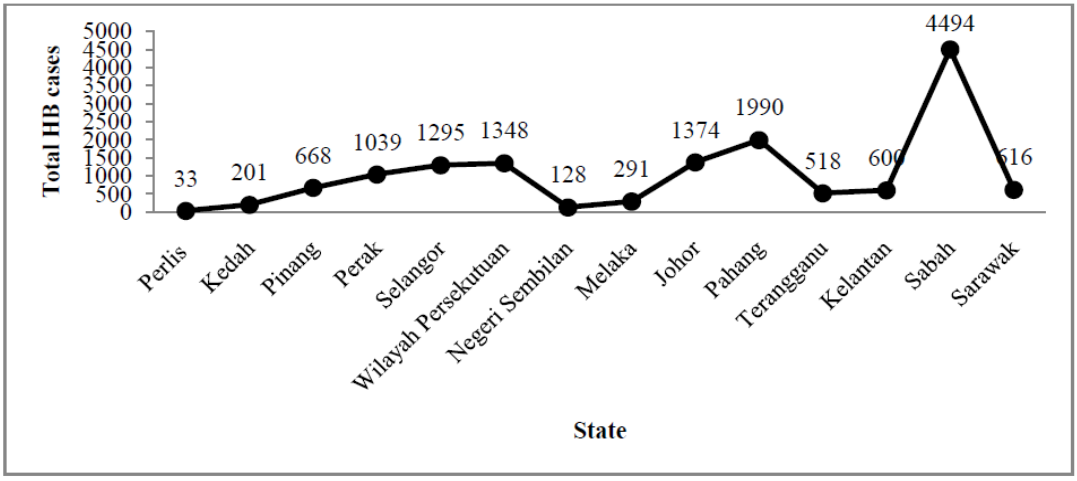

Figure 1.7: Hepatitis B cases in each state in Malaysia from 2003 until 2012 (Source: Raihan, 2016).

According to the Ministry of Health Malaysia, persistent HBV infection is a major factors of HCC whereby 80% of chronic HBV patients will develop into HCC (Azizah *et al*., 2019). Besides that, the risk of HCC is two to four times higher in men than in women with respect to family history, alcoholism and coinfection. Recent National Cancer Registry Report published in 2019 revealed that HCC is among the top ten leading cancers in Malaysia as shown in Figure 1.8. However, the incidence rate for men is two times higher compared to females (Figure 1.8). The cancer is more predominant in Chinese males and females compared to males and females from the other two major ethnic groups (Malays and Indians) in Malaysia (Figure 1.11 & 1.12). Surprisingly, most of the cancer patients with HCC are between the age of 25 until 74 years old (Figure 1.9 & 1.10) (Azizah *et al*., 2019). Overall, the incidence of HCC is

more common in males than females which is similar to the HBV prevalence where the ratio of males infected with HBV is two times greater than females. Thus, HCC report findings have a strong correlation with persistence hepatitis B infection.

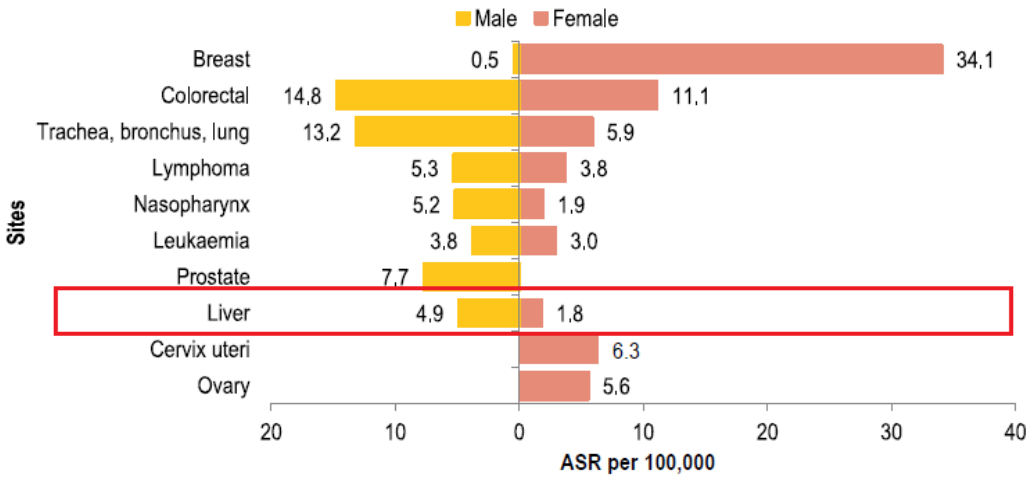

Figure 1.8: Age-standardised incidence rate for ten most common cancers, all residents, Malaysia, 2012-2016 (Source: National Cancer Registry Report 2012 – 2016, Ministry of Health Malaysia). HCC is ranked at top 10 cancer in Malaysia (refer to red box)**.**

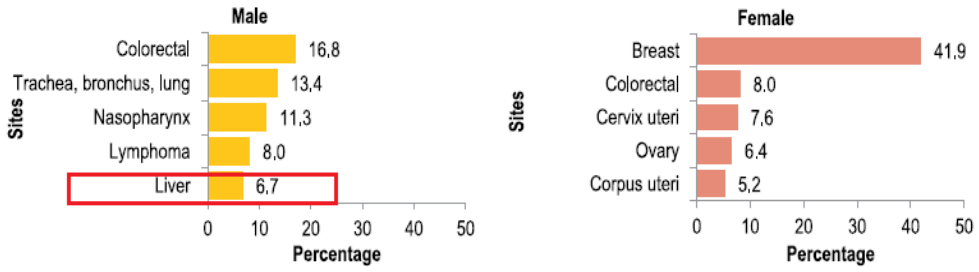

Figure 1.9: Common cancers among 25-59 years age group by sex, Malaysia, 2012-2016 (Source: National Cancer Registry Report 2012 – 2016, Ministry of Health Malaysia). **Note*:*** The incidences of liver cancer for males among 25 – 59 years is ranked at top five most common cancer (refer to red box)

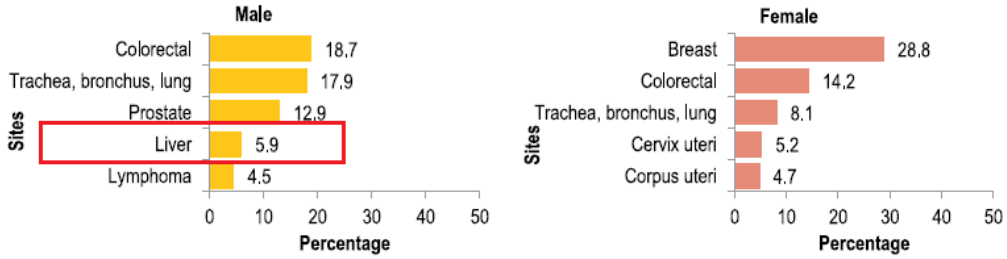

Figure 1.10: Common cancers among 60-74 years age group by sex, Malaysia, 2012-2016 (Source: National Cancer Registry Report 2012 – 2016, Ministry of Health Malaysia). The incidence of liver cancer for males among 60 – 74 years is ranked at top four most common cancer (refer to red box).

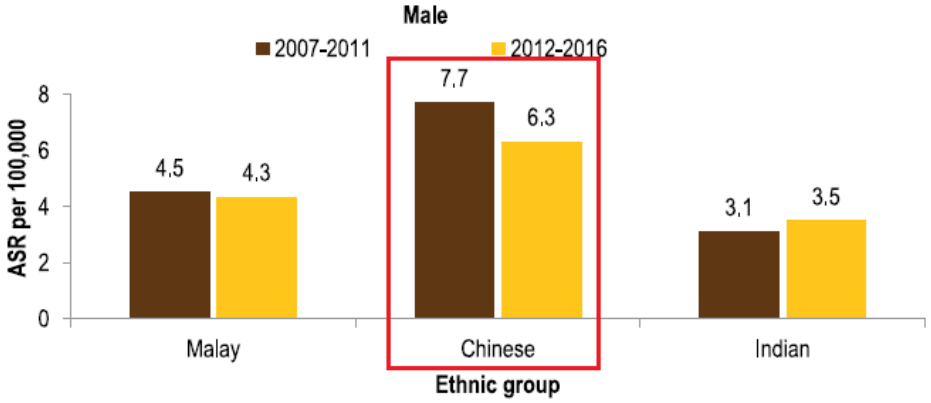

Figure 1.11: Comparison of age-standardised incidence rate of males by year and major ethnic group in Malaysia (Source: National Cancer Registry Report 2012 – 2016, Ministry of Health Malaysia). **Note*:*** The HCC incidences in Chinese males is higher compared to Malays and Indians. (refer red box).

Figure 1.12: Comparison of age-standardised incidence rate of females by year and major ethnic group in Malaysia (Source: National Cancer Registry Report 2012 – 2016, Ministry of Health Malaysia). The HCC incidences in Chinese females is higher compared to Malays and Indians. (refer red box).

1.4 Complication of HBV infection

There are several major complications of chronic hepatitis B infections known to be associated with HCC, chronic liver disease, liver fibrosis and cirrhosis. These factors include demographic factors, social factors, dietary and heredity factors as well as viral factors (Zamor *et al*., 2017).

In regard to demographic factors, most of the chronic hepatitis B male patients has higher chance to develops into HCC, liver disease and cirrhosis due to their lifestyle and social factors such as smoking and consumption of alcohol that contribute to liver damage (Chuang *et al*., 2009). Besides, age factors also play an essential role in development of HCC. For example, chronic HB infection patient with advancing age (elderly) has higher risk to develops into liver cirrhosis and HCC (El-Serag, 2012). Dietary also play an important role in HCC due to chronic hepatitis B infection. For instance, aflatoxin is a mycotoxin produced by fungi that grow on food such as corn

and peanuts that stored in warm and damp condition. International Agency for Research on Cancer has classified alfatoxin as one of the hepatocarcinogen that lead to HCC (El-Serag, 2012). Thus, intake of aflatoxin from the food especially in Asia and Africa countries is also known to contribute to a higher risk of HCC (Zamor *et al*., 2017).

Viral factors are another factor that contribute to the progression of liver cirrhosis and HCC. For example, viral co-infection is recognized as risk factors that contribute to HCC (Sunbul, 2014). Viral co-infection is a major lead to development of cirrhosis and HCC, for example HBV co-infection are HBV and HDV. Hepatitis D virus (HDV) occurs in the setting of hepatitis B infection as a coinfection due to its reliance on HBV for its replication. Hence, there is a heterogeneity as risk of HCC with HDV (Zamor *et al*., 2017). HDV able to promotes the course of progression to liver fibrosis and cirrhosis leading to development of HCC (Ringehan *et al*., 2017). In this circumstance, coinfection with HBV and HDV has greater risk of progressing to cirrhosis more rapidly as compared to monoinfected with HBV. Therefore, there is a causal relationship between viral factors and HCC.

HBV is a DNA virus also known as oncogenic virus that known to cause liver carcinoma. Approximately 90% of the world population sustain a-life-long asymptomatic and trivial clinical symptoms of this virus infection. HBV is reported to cause liver cirrhosis or HCC which is the most common liver disease in endemic regions (Ringehan *et al*., 2017). HCC is the most typical of primary liver carcinoma involving 75% to 85% cases of liver cancer. It is the sixth most common cancer and the second leading cause of cancer deaths worldwide (Rawla *et al*., 2018). However, CHB infection is the primary cause of HCC in Asia including Malaysia. In Malaysia, HCC is ranked

among the top ten common cancer according to Malaysian National Cancer Registry Report 2016 (Azizah *et al*., 2019). Figure 1.13 shows the disease progression of chronic hepatitis B infection.

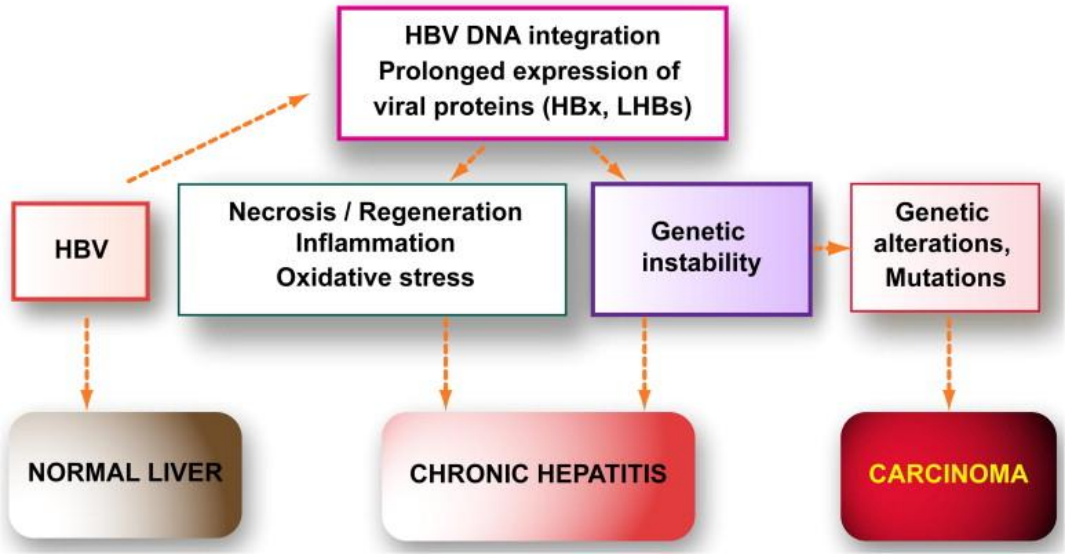

Figure 1.13: Chronic HBV infection and hepatocarcinogenesis (Source: Neuveut, Wei & Buendia, 2010). HCC occurs when the liver cells undergo genetic changes and mutation due to persistence hepatitis B infection. HBV DNA integration into the host genome and persistent expression of viral proteins such as HBx and large envelope protein (LHBs) can activate cellular cancer-related genes; induce oxidative stress and genetic instability. In the inflammatory context triggered by host immune responses, the viral functions contribute to ceaseless hepatocyte destruction–regeneration and provide a favourable ground for emergence of genetic and epigenetic alterations leading to hepatocyte transformation.

1.5 Pathogenesis of HBV

HBV is able to cause both acute and chronic liver infection (Valaydon & Locarnini, 2017). Acute hepatitis B infection refer to short-term illness that occurs within the first 6 months after an individual is exposed to the hepatitis B virus. The potential progression from an acute to a chronic HBV infection depends on age. Normally, 90% adults can clear the virus and recover without receiving treatment (Lok & Kaplan, 2007). Unfortunately, acute infection could lead to chronic infection if an individual failed to fight the infection. Chronic hepatitis B is a permanently or lifelong infection with the present of hepatitis B virus (Lok & Kaplan, 2007). As reported by Center of Disease Control and Prevention (CDC), majority of the children (90%) below 5 years old with HBV will develop into chronic infection while there is about 5 to 10% of adult infected with HBV will progress into chronic infection and the rest are able to recover without treatment (CDC, 2020). Over certain period of time, chronic hepatitis B can cause serious health complications such as liver cirrhosis and HCC (Figure 1.14). The pathogenesis of persistence HBV infection is complex due to multifactorial, stages and eventually progress into liver complication as seen in Figure 1.15 below (Jayalakshmi *et al*., 2013).

Generally, HBV is not cytopathic to hepatocytes. The pathogenesis of both liver damage and viral control are due to immune mediated response (Valaydon & Locarnini, 2017). HBV induced liver fibrosis, cirrhosis and HCC development is a multi-steps process that may progress over 20 – 30 years and involves number of stages such as establishment of chronic HBV infection, chronic liver inflammation, progressive liver fibrosis, initiation of neoplastic clones causes genetic alterations and progression of malignant clones leading to hepatocarcinogenesis (Figure 1.15). The clinical outcome

of infection is depending on the interaction between HBV replication as well as host immune response. HBV is a feeble inducer of the innate immune response. Therefore, acute infection is predominantly mediated through the adaptive immune response. As reported by Trépo *et al* in 2014, people with serological recovery from acute HBV infection have strong T-cell responses to several epitopes in different regions of the HBV genome whereas patients chronically infected with HBV have weak T-cell responses to a few epitopes (Trépo *et al*., 2014).

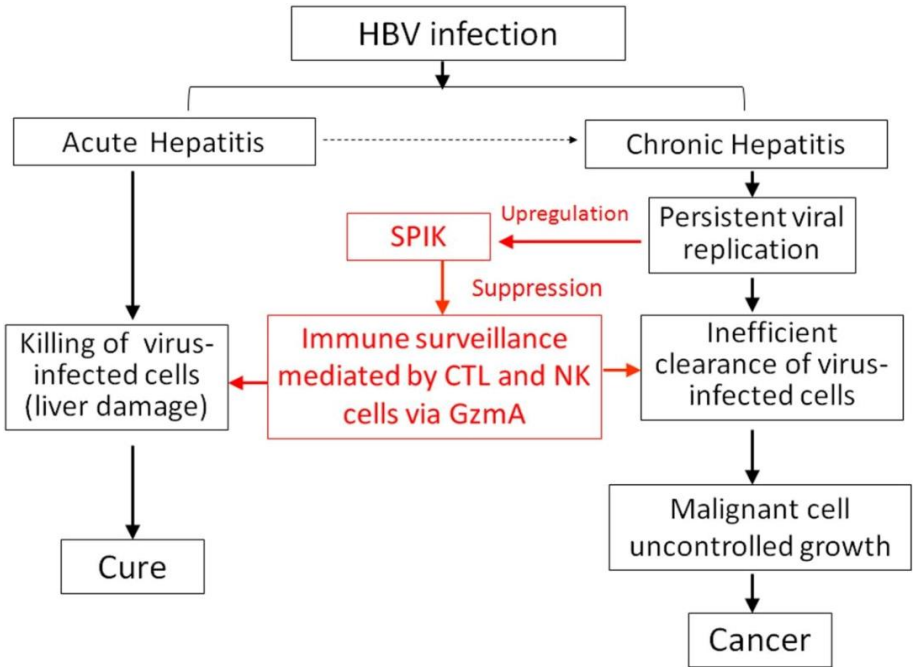

Figure 1.14: Pathogenesis of HBV infection and liver disease (Source: Lu, 2011).

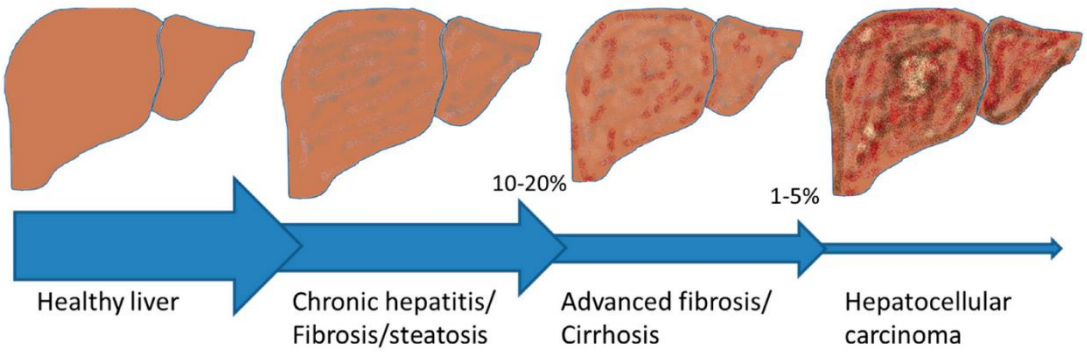

Figure 1.15: Stages of pathogenesis due to HBV infection (Source: Jayalakshmi *et al*., 2013) Prolonged chronic HBV infection will develop into liver cirrhosis and HCC

1.6 Clinical and laboratory diagnosis of HBV

Hepatitis B infection is a serious global infectious disease, thus appropriate and accurate diagnosis of HBV is important for treatment and management (Al-sadeq *et al*., 2019). According to the Centers for Disease Control and Prevention (CDC), there are several tests available for HBV clinical diagnosis. The interpretation of each test is as follow (Table 1.2)

Table 1.2: The type of laboratory diagnostic tests of Hepatitis B virus (HBV)

Marker(s)	Interpretation
Hepatitis B Surface Antigen (HBsAg)	Detection of protein present on the surface of the hepatitis B virus
Hepatitis B Surface Antibody (anti-HBs)	Detection of antibody produced by the body in response to the hepatitis B surface antigen
Total Hepatitis B Core Antibody (anti-HBc)	Measure an antibody produced by the body in response to hepatitis B core antigen
Hepatitis B "e" Antigen (HBeAg)	Measure protein found in the blood when the hepatitis B virus is present during an active hepatitis B virus infection.
Hepatitis B e Antibody (HBeAb)	Detect antibody that is produced by the body in response to the hepatitis B "e" antigen.
Hepatitis B Viral DNA	Detect the presence of hepatitis B virus DNA in a person's blood. This test is also used to monitor the effectiveness of drug therapy for chronic hepatitis B virus infection.
IgM Antibody to Hepatitis B Core Antigen (IgM anti-HBc)	Detect an acute infection of HBV

Source: Centers for Disease Control and Prevention (CDC) 2020

1.7 Treatment and Prevention of HBV

HBV is preventable by vaccination. Therefore, vaccination is the cornerstone for prevention of HBV. Various studies have shown that the incidence of acute hepatitis B, chronic hepatitis B and chronic liver disease as well as HCC is successfully decreased in the HBV vaccinated population (Ringehan, McKeating & Protzer, 2017). In 1989, HBV vaccination was introduced in Malaysia and Ministry of Health Malaysia, implemented hepatitis B vaccination program for all infants born in 1989 onwards (Raihan, Mohamed, Hassan & Said, 2017). The schedule and doses of vaccination given to the infants are three doses, first dose is given at birth, followed by second dose at one month old and third dose at six month of age respectively (Raihan *et al*., 2017). Besides that, vaccination should be provided to high-risk population group such as healthcare workers, blood donors, public health workers and drug users to boost their immunization (Yin & Tong, 2006). Other than vaccination programme, implementation of Hepatitis B screening programme is another way for HBV prevention. According to the national strategic plan for hepatitis B and C (NSPHBC) 2019 – 2023 from Ministry of Health Malaysia, all of the high-risk groups namely healthcare workers, blood donors, foreign workers and drug users are main target to perform hepatitis B screening (NSPHBC, Ministry of Health Malaysia, 2019). As stated by World Health Organization (WHO), the initiative of implementing various strategies in HBV prevention able to reduce the rate of new infection (WHO, 2019).

Currently, there is no effective treatment for chronic hepatitis B infection in the world. Both alpha – interferons (αIFNs) and nucleosides analogues (NA) antiviral therapy are used to treat and control HBV infection. Alpha - Interferons therapy is an immunomodulatory agent that can be used to harness the immune clearance of HBV but it is not effective as NA (Seeger & Mason, 2016). The rationale of using NA

antiviral drugs is to inhibit HBV viral replication and suppress the viral load thus, it can attenuate chronic hepatitis B infection (Grimm *et al*., 2011). To date, there are several types of oral antiviral drugs available for hepatitis B treatment namely tenofovir, entecavir, telbivudine, lamivudine and adefovir (Raihan *et al*., 2016). These treatment strategies have shown significant benefits for CHB patients in disease control, improve the quality of life and survival outcomes (Grimm *et al*., 2011).

1.8 Rationale and Significance of the Study

Viral hepatitis B infection is a major global burden nowadays. It is one of the emerging viral diseases in Malaysia, however many knowledge gaps need to be addressed to control this viral infection effectively in the future. In order to identify and understand the diseases condition of viral hepatitis B, it is very important to know the prevalence and current trends of viral hepatitis B in Malaysia and particularly in Kelantan.

Currently, there is limited study carried out on hepatitis B infection and the risk factor associated with viral hepatitis B in Kelantan. Hence, this study will address the past and current issues of viral hepatitis B cases in Kelantan. Conducting prevalence and epidemiology study could provide a better and accurate information regarding the disease burden in Kelantan. Besides, majority of the public remains unaware about the incidence of hepatitis B infection mainly due to the paucity of information related to this disease. Therefore, establishing a baseline data for viral hepatitis B is very important for the public awareness regarding the current scenario of the cases especially in Kelantan.