1. INTRODUCTION

Hepatitis B is the most common infectious disease caused by Hepatitis B virus (HBV) that can leads to liver cirrhosis and hepatocellular carcinoma (HCC). (Karan et al., 2002) According to World Health Organization (WHO) documentation, 257 million people worldwide infected with HBV infection and its complications such as cirrhosis and hepatocellular carcinoma resulted in 887,000 deaths during 2015. (WHO, 2017) Every year about 6,000,000 people die due to the acute or chronic consequences of hepatitis B (WHO, 2008) It is estimated that 15% to 40% of HBV chronic carriers can develop cirrhosis, hepatocellular carcinoma and end-stage liver failure. (Russo FP et al., 2015) India is the second largest global pool of chronic hepatitis B viral infection. (Datta S et al., 2008)

The seroprevalence of HBsAg (Hepatitis B surface antigen) is 3.9% globally. (Razavi-Shearer D et al., 2018) HBV endemicity is divided in to 3 categories based on HBsAg prevalence rate. Highly endemic areas includes China, South East Asia, Indonesia, and sub-Saharan Africa, more than 8% of the population are reported with chronic HBV infection. Intermediate areas include South America, South West Asia, Eastern and Southern Europe, show chronic HBV infection rate between 2% and 7% of population. Low endemic regions include developed countries, such as North America and Western Europe and the HBV prevalence rates range from 0.5% to 2%. (Ott JJ et al., 2012) Based on many epidemiological and molecular studies worldwide, HBV is one of the most significant infectious diseases. (Mauss et al., 2013)

Blumberg and co-worker were first identified HBV infection in 1965. (Blumberg et al., 1965) Hepatitis B virus is a non- cytopathic viral pathogen belongs to the Hepadnaviridae family and it is a partially double stranded DNA virus with 40 to 42nm in size. (Chang et al., 2007; Di Marco V et al., 1999; Marion PL et al., 1988) The viral genome comprises a complete coding strand (negative strand) and an incomplete non-coding strand (positive strand), that replicates by reverse transcription through an RNA intermediate. (MariaKuttikan Jayalakshmi et al)

HBV infection results in a broad spectrum of disease outcomes. Acute hepatitis B is defined as a short- term infection which occurs within 6 months after a person gets infected with the virus. The infection ranges from mild illness with few or no symptoms. (CDC, 2017) Symptoms of acute HBV infection can occur after an incubation period of 2- 3 months, including nausea, jaundice,
upper abdominal pain and malaise. The symptoms developed by acute HBV infection is age dependent; less than 10% of children and among adults about a third of those infected develop symptoms. (Edmunds WJ et al., 1996; Ramsay M et al., 1998; McMahon BJ et al., 1985) And 90% of infants’ gets infection perinatally develops CHB infection. (Edmunds WJ et al., 1993) Persistence of HBsAg for atleast 6 months with or without concurrent HBeAg indicates chronic hepatitis B infection. About 20 to 30% of adults with chronic infection can develop cirrhosis and/or hepatocellular carcinoma (Raimondo G et al., 2008)

The transmission of HBV occurs through sexual contact, percutaneous or permucosal exposure of blood and body fluids from an infected person. At the time of delivery, perinatal transmission occurs. (Remington et al., 2006) Transmission of HBV is also acquired with in household through close non sexual contact. (Davis LG et al., 1989) The medical procedures such as surgical and microsurgical procedures (35.6%) (Essam M et al., 2010), accidental puncture by infected needle (10- 30%) (Petruzzello et al., 2016), whole blood transfusion (14.8%) (Eduard et al., 2014), haemodialysis, intravenous (i.v.) drug application (14.8%) (Razia Khatoon et al., 2016), accidental contacts with infected blood are the risk factor associated with HBV transmission.

The non- medical procedures like tattoo (44.2%) (Eduard et al., 2014), or piercing cosmetic procedures (9.4%) (Eduard et al., 2014), manicure or pedicure and shared use of razor or toothbrush are the high risk factors responsible for the transmission of HBV from infected person to others. (Veseliny E et al., 2014; Lok A.S et al., 2007) Healthcare workers (HCW) 18.2% (Garima et al., 2013) gets infected by HBV through direct contact with infectious materials such a HBV – infected blood or body fluids (Mueller A et al., 2015) The virus is not transmitted through breast feeding, sharing eating utensils, hugging, kissing, holding hands and coughing or sneezing. (CDC, 2008)

Diagnosis of HBV is established by demonstrating specific antibodies or antigen in serum of patients. (WHO, 2002) Serological markers for the diagnosis of HBV infection include HBsAg, antiHBs, antiHBC- IgM, antiHBC- IgG, HBeAg and anti HBe (Kramvis A et al., 2014). Presence of HBsAg indicates that the patient is highly infectious. After the acute infection, antibody to HBsAg (antiHBs) develops in 80% of cases and this indicates immunity. (Cunninghan F et al., 2005) Presence of Immunoglobulin M (IgM) to HBcAg in acute infection and Immunoglobulin G (IgG) in chronic infection helps to differentiate the patient into acute and chronic infection. (Kasper D et al., 2005) Hepatitis B e Antigen (HBeAg) is an important marker of transmissibility which arises during
acute and in certain patient with chronic phase. Antibody to HBeAg (anti- HBe) becomes detectable when HBeAg is lost and is associated with low infectivity. (W. Levinson EJ et al., 1998)

For Acute hepatitis B infection, there is no specific treatment. Oral antiviral drugs are used for the treatment of chronic hepatitis B infection. Treatment does not cure the infection, but helps to suppress the replication of the virus and improve long term survival. (WHO, 2018) Patients with acute hepatitis, the virus get cleared and developed a strong host immune response against HBV antigens. In chronic HBV patients the host immune response becomes weak and the virus remains in the body and leads to chronic complications. (Chisari FV et al., 1995) Cirrhosis and hepatocellular carcinoma are the main sequelae of CHB infection. (Chen C J et al., 2006) Patients with 5 year risk of cirrhosis along with CHB viral infection ranges from 8-20%. (EASL et al., 2012) The annual risk of hepatocellular carcinoma in CHB patients ranges from 0.1 to 10% and it is mainly depend on the different stages of liver disease. (Chu et al., 2000)

Several factors are involved in the disease progression of HBV infection (persistence and clearance) such as virological factors, genetic factors, immunological factors and environmental factors but the exact mechanism is not clearly understood (Thursz M. et al., 2000; Chisari FV et al., 1995)

Several immunogenic factors involved in viral hepatitis. Genetic predisposition studies may help early detection of chronic HBV infection and prevention of its complication (cirrhosis and liver cancer). Major histocompatibility complex (MHC) plays an important role in host immunity, and it helps in clearing the virus-infected hepatocytes. It has the capacity to attract and bind viral peptides, hence the Human leukocyte antigen (HLA) genes has been focussed on many studies because they modulate the immune response by presenting antigen to T cells. (Moradpour and Blum et al, 2002)

HLA is a protein that presents self and non-self antigens to T cell receptors to sustain self-tolerance and adaptive immunity. It is located on the short arm of chromosome 6, designated as 6p21.3. It has more than 200 functional and non-functional genes. It is about 3.6 Mb in length. (Nature, 1999; Shiina et al., 1999) Heterozygosis and gene polymorphisms at HLA loci enable HLA molecules to present a wide array of antigens and diversity. (Martin MP et al., 2005)

Cellular immune response is mediated by highly polymorphic HLA class I and II molecules and are associated with the outcome of any acute or chronic viral infection. (Singh R et al.,
Various populations bear different HLA alleles proved that HLA polymorphism associated with the outcome of HBV infection. (Viruses, 2012 edition) HLA class II molecules act against the viral infections through effective presentation of viral antigens to CD4+ helper T cells that helps in stimulation of cytokine release. And also to CD8+ cytotoxic T lymphocytes, helps in recognition of viral epitope in combination with HLA class I antigen co-expressed on hepatocytes, a process of viral clearance and viral persistence (Moradpour and Blum et al, 2002)

Various research studies proved that link between HLA polymorphism and HBV pathogenesis may help in the potential therapeutic targets for hepatitis B. (Viruses, 2012 edition) Even HLA association with HBV infection plays an important role for designing host specific therapeutic strategies. Hence, HLA genes are directly involved or closely linked as a genetic marker for true susceptibility, protection and treatment response. (Milich D et al., 2003)

The pathogenesis of HBV remains unclear. Along with the viral and environmental factors, host genetic factors leading to the pathology of disease regression or progression. The host-virus interaction resulting in acute or chronic viral infection depends on cellular immune responses that are regulated by the host’s HLA type and HLA restricted viral escape mutants. Interchange of antibody secreting B-lymphocytes, HLA restricted T lymphocytes, cytokines and NK cells disorders the immune response to viral infections. HLA class I and class II molecules presents viral antigens to CD8+ T cells and CD4+ T cells respectively and further the viral clearance or persistence. (Martin MP et al., 2005)

The availability of data on HLA in Hepatitis B viral infection is scanty in the Indian study. At the time of design of my study, the published Indian study showed HLA DRB1*15 allele to have the strongest association with HBV outcome in the Western Indian population. (Amarapur et al., 2003) A study from Vellore showed that HLA DRB1*07 allele is associated with HBV chronicity in the South Indian Population. (GJ Fletcher et al., 2011) Association of HLA DQ and DP alleles with HBV infection has not been studied in the Indian population. So, this study was taken up to detect the frequency of HLA DRB1*07:01, DQB1*03:01 and -DPB1*09:01 alleles and their association with HBV infection.