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Review Article

Global and Indian distribution of hepatitis B virus (HBV) genotypes/sub-genotypes

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Abstract

Hepatitis B virus (HBV) infection is a serious global public health concern in the modern era. It was estimated around 2 billion individuals throughout world are affected with HBV and 350 million of them suffers from a chronic infection. India is the most broadly diversified nation in identity and social distribution. Furthermore, high endemic migrations, high birth rate and drug abuse are the reasons particularly important contributors to enhance the epidemiology of HBV, particularly in comparison to the eastern and northern regions of India.

HBV genotypes A, D and C have been well defined from different parts of India. However, data regarding the molecular epidemiology of HBV in India is still scanty for early prediction of the disease and its severity. This publication reviews the existing information on the genetic diversity of HBV genotypes and subgenotype in India and globally as well as their relationship with the progression of the disease. Furthermore, the HBV epidemiology in different regions of India has been significantly impacted due to the recent increase in improper psychoactive drug usage.

Genotype specific pathophysiology of HBV may result into differential clinical outcomes in chronic patients around the world. Lower rates of spontaneous HBeAg sero-conversion found in patients infected with HBV genotypes C and D. The lifetime risk of cirrhosis and hepatocellular carcinoma (HCC) was greater in genotypes C and D than in genotypes A and B. Core promoter and pre-S mutations have been responsible for an increased risk of HCC.

Keywords: Hepatitis B virus genotypes, HBV prevalence, Hepatitis B virus epidemiology, Hepatocellular carcinoma, Nucleotide analogue treatments.

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1. Introduction

Hepatitis B virus (HBV) is the most significant cause of liver malfunction among all critical illness throughout the world. HBV infection is regarded as life threatening disease due to its high rate of mortality.[1] An estimated 304 million individuals worldwide are infected with HBV and around 95% of all hepatitis-related fatalities are caused by hepatocellular carcinoma (HCC). The World Health organization (WHO) reported that approximately 13 lacs people died due to hepatitis infection in the year 2022 globally, which was the second highest cause of death among all kind of viral infections.[2] The distribution of hepatitis prevalence and burden varies by area. It was reported by WHO that African countries participate 63% of all new instances of hepatitis B positive cases and 18% of neonates received vaccination immediate after birth followed by Western Pacific Region accounts for 47% of mortality due to hepatitis B.[3] People belongs to southern regions of the Middle east and Eastern, Central Europe are considered as moderate HBV endemicity. Australia, North America, Western and northern Europe are the regions categorized as low endemicity.[4] In most of the countries; prevalence of chronic HBV varies in between 2% to 20%. HBV has a diversified clinical manifestations which includes inactive carrier state, HCC, chronic hepatitis and liver cirrhosis, between 15% and 40% of HBV carriers will eventually be at risk of developing the same.[5]

In Indian scenario, there are various reasons why hepatitis is so widespread in India and it's a major health concern. According to the survey done in 2019 & 2021 by

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National health survey 3-4 under the supervision of National Viral Hepatitis Control Program (NVHCP), there were 164,826 instances with national sero-prevalence of Hepatitis B was 0.95%in India. The states who had the maximum prevalence of hepatitis among 164,289 cases reported in 2019 within India are Uttar Pradesh, Bihar, Madhya Pradesh, Punjab, Delhi, Uttarakhand, Haryana, Maharashtra, and Rajasthan.[6,7]

Table 1: Global geographical distribution of HBV Genotypes

Genotype	Patel A *et al.* 2024[10]	Sunbul M 2014[11]	Al-Sadeq DW *et al.* 2019[1]	Lin CL *et al.* 2015[5]	Kumar R *et al.* 2011[12]	Liu Z *et al.* 2021[13]
A	Europe, North America, and some parts of south eastern Africa, central and South America	India, Japan, Spain, Morocco, Central Africa, Brazil, Nigeria, Gambia, Rwanda, Cameroon	Asian continent, Europe and Africa, Saudi Arabia, Oman	Sub-Saharan Africa, India, Northern Europe, Western Africa	European origin, Belgian, France, Central Poland, Saudi Arabia, Serbia, Central African Republic, Romania, Pakistan, Brazil, China	south-eastern Africa, north-western Europe, and some countries in America, Brazil, Cuba, and Haiti
B	Asia, China, Taiwan, and Southeast Asia	China, Indonesia, Vietnam, Taiwan, Hong Kong, Philippines, Canada, Thailand,	-----	Japan, East Asia, Taiwan, China, Indonesia, Vietnam, and the Philippines, Alaska, Northern Canada, and Greenland	Southeast Asia, Surabaya, Indonesia, Malaysia, Pakistan, Thailand, Taiwan, China	Southeast Asia, China, and Japan
C	Asia, Japan, Korea, and China.	China, Indonesia, Vietnam, South Korea, Hong Kong, Japan, Philippines, India, Canada, Thailand, Australia	Oman	Taiwan, China, Korea, and Southeast Asia, Australia, The Philippines and Vietnam, Indonesia	Vietnam, Southeast Asia, Korea, China and Spain, Malaysia, Saudi, China Arabia, Pakistan, Thailand, Taiwan	Southeast Asia, China, and Japan, South Korea
D	Found globally, mostly predominant in the Mediterranean basin, Middle East, and parts of South Asia	Tunisia, Turkey, India, Canada, Central Africa, Saudi Arabia, Iran, Mongolia, South Africa, Italy, Morroco, Egypt, Pakistan, Australia, Spain	Middle East, Saudi Arabia, Oman, Egypt, Iran	Africa, Europe, Mediterranean countries, India, and Indonesia	Soviet Union and Eastern Europe, Moscow, Russia, Malaysia, Belgian, Afghanistan, Central Poland, Saudi Arabia, Serbia, Central African Republic, Romania, Pakistan, Brazil, China	Mediterranean basin and some parts of Asia, such as Western, Central, and South Asia, Brazil, Cuba, and Haiti
E	West Africa and central Africa	Central Africa, Saudi Arabia	West Africa, Saudi Arabia, Oman, Egypt	West Africa	Saudi Arabia	West and central Africa
F	South and central America, Mexico	Tunisia, Brazil, Spain, Argentina	----	Central and South America	Brazil, China	South and Central America

Table 1 Continued…						
G	United States, Europe and some parts of Asia and Africa	----	----	France, Germany, and the United States	France	Mexico
H	central and South America, particularly Mexico and Guatemala	----	Central America	Central America	----	Mexico
I	Southeast Asia, particularly Laos and Vietnam	Vietnam	----	Vietnam and Laos	----	----
J	Ryuku Islands of Japan	----	----	Japan	----	----

2. Geographic Distribution and Genetic Diversity of HBV

HBV is a member of Hepadnaviridae family, which includes several genera with double-stranded DNA genome.[8] In HBV replication, covalently closed circular DNA (cccDNA) serve as transcriptional template for viral pre-genomic RNA and messenger RNAs within the nucleus of host cell.[5]

In HBV genomes, sequence heterogeneity is very high, Over 10 genotypes from A to J along with 40 genetic subgroups or even more have been discovered in HBV genomes worldwide. While a large number of viral

Table 1 the majority cases are found in Asia, including China, Japan, Indonesia, and are inhabited to HBV genotypes B and C, while Genotype D is more prevalent in the Middle East, Mediterranean geographical area and in India. Distribution of genotype E is more common in India and sub-Saharan Africa. There were very few cases of HBV/F and HBV/H strains have been identified only in Central and South America. HBV/G has been detected in France, Germany, and the United States. Furthermore, Rajesh Kumar *et al.* have observed genotype I from the Northeast Indian primitive tribe.[12,14]

Despite the significant global prevalence of genotypes A, B, C, and D, the distribution of HBV genotypes H, I, J are notably lesser prevalence rate as shown in **Table 1**. There are very few studies reported genotype J but the study conducted by Chih-Lin Lin *et al* reported the same genotype only in Japan. Vietnam population has diversified with genotype B, C and genotype I, which was reported underrated in most of the countries. Countries with the most diversified population infected with HBV are China, India, and Japan.

A study conducted in the year 2014 by Ismail M.A *et al.* shows the notable difference in between frequency and distribution of HBV sub-genotypes in Indian sub-continent.[15] Furthermore, subgenotype C1 (86.2%) and C2 (83.3%) was found higher in the eastern & north-eastern region of India followed by subgenotypes D1, D3, and D5 were identified in distribution of mutants have also been reported because of abnormal reverse transcriptional replication process through RNA intermediates and the inability of proofreading of its viral polymerase, A research conducted by Chih-Lin Lin *et al.* shows that majority of the strains of HBV in Taiwan are of genotypes B and C and might be possible that parents and their children have the same HBV genotype. Consequently, genotyping data simply was unable to determine the children's viral origin (**Table 1**).[9]

Genotype A is the most prevalent variation across Europe, Africa, and India. According to

between 74% to 94% respectively.[16] The southern region has the highest prevalence of HBV subgenotype D2 (68.7%). Genotype D was identified to be more prevalent in northern India than genotype A. This was comparable to the HBV genotype distribution found in southern and western India.[17] There are some difference in the geographical variation of genotypes C and D subgenotypes.

3. Distribution of HBV Sub-genotypes Worldwide

It has been described that recombinant HBV strains such as HBV C/D, HBV A/G, and HBV D/E occur due to the co-infection result of different genotypes. Many researchers illustrated that clinical outcome and prognosis of treatment response may vary in patients all over the world because of HBV genetic diversity with different HBV (sub) genotypes in certain geographical areas. This article aids in improving knowledge of the linkage between clinical outcomes and different HBV genotypes.[18]

It is clear from the currently available data that HBV genotypes and subgenotypes can have a substantial impact on viraemic levels, HBeAg sero-conversion rates, and mutational patterns that may have a substantial impact on the variety of clinical symptoms and even the responsiveness to the medication used to treat viral infections. Even more intriguing is the appearance of the most extensively researched clinically significant mutations.

Table 2, showed that subgenotype A2 is more common in Europe, America, and Japan (Asia), but subgenotype A1 is more common in Asia and southeast Africa. Subgenotype A3 is common in central and western Africa, while Haiti (North America) is home to subgenotype A5. In Genotype B, subgenotype B1 is prevalent in Japan (Asia), B2 is present in the majority of countries and B6 is prevalent in Canada (North America). Subgenotypes B3, B7, and B9 are restricted almost entirely to Southeast Asia, especially Indonesia and Malaysia. While subgenotype C2 is more abundant in East Asia, North America, and Oceania, subgenotype C1 is more common in South and Southeast Asia. Subgenotype C5 prevails in the Philippines and its neighboring countries, among all the subgenotypes of Genotype C, C6 is mostly found in Indonesia and Papua New Guinea. In Genotype D, Subgenotype D1 is widely distributed in all continents, but is highly prevalent in Asia, and D2 is dominant in Europe, Bangladesh, and India. Subgenotype D3 is frequent and appears to be present worldwide, while D5 is only found in some Asian countries. Subgenotype D7 is prevalent in Brazil, Cuba, and Africa. There are insufficient evidences regarding subgenotypes of Genotype F available to estimate the prevalence because it is restricted in almost all parts of the world only few studies reported that 4 subgenotypes of genotype F. Having evolved distinctly in certain geoethnic group, HBV genotypes/subgenotypes have a distinct geographical distribution pattern.[11,19,21]

Table 2: Continents wise distribution of HBV Sub-genotypes

Continents	HBV Sub-genotypes distribution	Reference
Europe	A2, D1-D4	Pourkarim MR *et al.,*[22] Thijssen M *et al.*[23] & Olinger CM *et al.*[24]
North America	1a, 1b, 2a, 2b, 2c and 3a	Olinger CM *et al.*[24]
South America	A1, A2,, F4, F1, F2,F2a, D3	Reuter et al.,[19] Wolf JM *et al.*[25] & Araujo NM et al.[26]
Asia	A1, B2-5, B7, B9,C1, C2, C3, C4, C5-16, D1,D2,D3,D4	Potter BI *et al.,*[20] Lin S*et al.,*[21] Kyaw *et al.*[27] & A.A.AI-Qahtani *et al.*[28]
Africa	A1-A7, D1, D2-D4, D7-D8	Kafeero *et al.,*[17] Thijssen M *et al.* [23] & Hannachi N *et al.*[29]
Oceania	C4, D4	Liu Z *et al.*[13]

4. HBV Epidemiology in India

South Asia, including India faced significant fatality rates every year due to several infectious diseases. Millions of people in India are at a risk from chronic hepatitis B, HIV and tuberculosis. Now India ranks second globally in terms of population affected by HIV infection and AIDS, indicating a rapid shift in the virus epidemiology of transmitted through prenatal or sexual routes.[30] These illnesses are quite common in many South Asian countries are attributed to factors such as poverty, unhygienic living conditions, illiteracy, unsafe blood supplies, and inadequate hospitality, multiple use of same needles/syringes, risky sexual behaviours, and frequent intravenous drug use.[31]

The World Health Organization's report on hepatitis B virus (HBV) prevention in India indicates that the prevalence of HBsAg in the general population ranges from 0.1% to 11.7%, with the majority of studies demonstrating frequencies in between the 2%–8% range, but the HBsAg prevalence among the blood donors varies from 1% to 4.7%.[32] Although, some North Eastern states exhibit higher positivity around 7%, other parts of India show no substantial geographical change. Approximately, 50 million HBV carriers are thought to exist in India with an average of 5%, representing nearly 15% global pool of HBV carrier and making it the second highest populated country among chronic HBV infections globally.[33] Conservative approach suggested that over 9 million people in India will acquire HBV infection at some point in their lifetime, around 1.5 million developed chronic HBV infection and nearly 2 million died from acute or chronic HBV-related complications.[34]

Few primitive tribes in Andaman and Nicobar Islands have shown unusual high positivity rates of HBsAg in contrast to mainland India. According to studies, there is a hyperendemic of HBV infection; the Nicobarese have a carrier HBsAg of 23.3% followed by Shompen 37.8%, the Karen 11.6%, and the Jarawa tribe has a 65%. The highest documented prevalence rates of HBsAg worldwide are seen in the Jarawa tribe.[35-37]

India's vast and diverse population comprises various racial communities with distinct cultures, ethnicities, dietary habits, and lifestyles, which leads to a wide range of infectious and chronic disease patterns. India’s geographical location revealed different HBV genotype variations between West, Central and East Asian countries. The Indian population has significant genetic, geographic, and sociocultural variety as a result of historical anthropological migrations. Additionally, the distribution of HBV genotypes may be significantly impacted epidemiologically by India's more than 200 years of colonial rule.[1] The different distribution of HBV genotypes in the different regions of the countries reflects this multi-ethnic background (**Figure 1**). Furthermore, recent increases in trade, drug and international travel has been significantly impact the epidemiology of HBV and other perinatal transmission of infections in India, particularly in the eastern and north-eastern regions.[39]

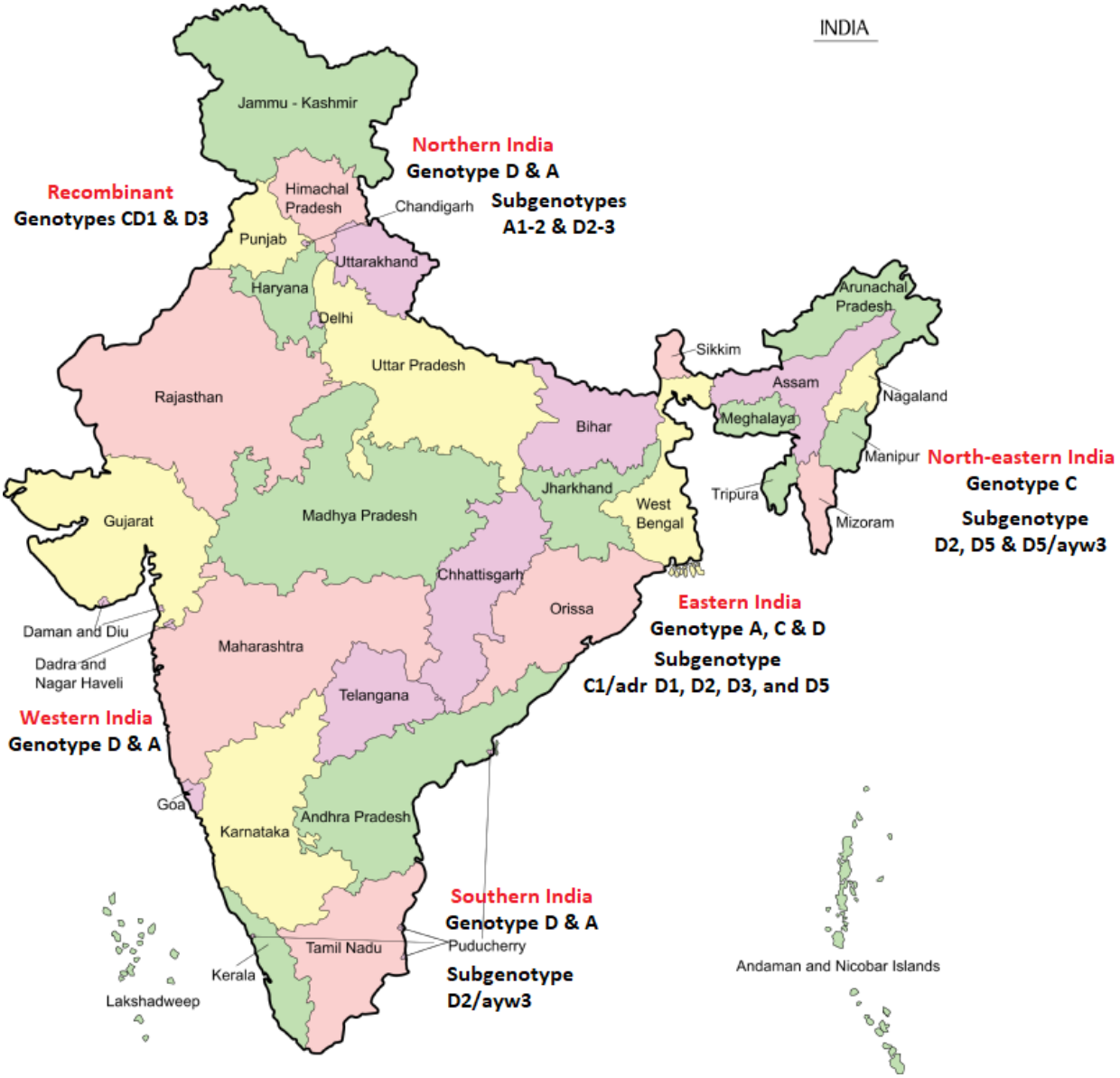

Figure 1: Geographical Distribution of HBV genotypes/subgenotypes in India[15,16,40-42]

In Uttar Pradesh, North India HBV genotype D is the most prevalent which covers around 78-80% among HBV infections leads to chronic hepatitis while genotype A reported only in 20-22% cases. Although there is insufficient data to determine the precise prevalence of its genotypes and sub-genotypes in the eastern region of Uttar Pradesh, it has been reported in many Indian research that genotypes A and D are the most prevalent among all variations. According to a study by Sibnarayan Datta, northern India has an equal prevalence of genotypes A and D.[42] In another study conducted by Salman Khan *et al.* from Meerut, Uttar Pradesh, India found that the genotype B and genotype A were found to be 68.8% and 31.25%, respectively.[43] The studies conducted so far has revealed genotype D as predominant genotype over genotype A.[44] Till now, very limited research has been conducted to investigate the epidemiology and genetic diversity of HBV in eastern and other regions of Uttar Pradesh.

5. HBV Gene Mutation Mechanism for Diversity

A significant factor that makes HBV incurable is the complex form of HBV mutation. High mutational rate found in HBV in comparison with other DNA viruses, it was calculated at 1.4 × 10-5 to 3.2 × 10-5 nucleotides per site per year. In addition to a number of other reasons including the virus's inherent traits, host immunological pressure, and selective pressure from antiviral therapies, HBV is a highly variable virus whose evolution and variation follow theory of natural selection and random drift leads to a wide range of genetic variations which includes different genotypes, subgenotypes, and quasispecies. The main cause of HBV diversity is the reverse transcription process that occurs during HBV replication, which gives its trait comparable to RNA viruses.[45]

5.1. Factors influence genetic diversity

There are several important factors responsible for genetic diversity of HBV. Some of these are listed below as:[46]

1. Dominant and resistant gene can become advantage for a patient.
2. Drug-resistant mutations may arise as a result from antiviral therapies. Genotype and subgenotype variations can influence disease severity and response to treatment.
3. The host's immune system can also drive the evolution of HBV, favouring variants that evade immune clearance.
4. The existence of different HBV genotypes (A-H) across the world contributes to the overall genetic diversity.
5. Exchange of genetic information between HBV genotypes due to recombination and this is also the cause of diversity.

6. Methods to Detect Genetic Mutation

There are various methods and techniques to detect viral mutations and quantification for the comprehensive analysis of genetic mutation and diversity of gene variants. Recent techniques like sequencing methods (Direct and Next Generation sequence) have made it easier to detect HBV DNA mutations. Many other sensitive and high throughput techniques can be used to detect genomic mutations in HBV. Allele-specific oligonucleotide hybridization (ASOH), Amplification refractory mutation system (ARMS), clone-based sequencingand multiple real time Polymerase chain reaction (RT-PCR) amplification techniques enabling detection of mutations even at low frequencies of viral quasispecies. Restriction Fragment Length Polymorphism (RFLP) uses restriction enzymes to cut DNA at specific sites, allowing for detection of mutations that alter the restriction sites.[47]

7. Effects of HBV Genotypes and Sub-Genotypes on Clinical Practice

High replication rates and the capacity to evade immune clearance, HBV genotypes may influence the prevalence by affecting replication rates. HBeAg is more prevalent in individuals with genotype C than in those with genotype B, indicating that HBeAg clears more rapidly in genotype B patients.[48] A relationship has been identified in between abnormal liver enzymes level and HBV genotype, which are less common in hepatitis B carriers with genotype B than in those with genotype C.[49] However, several studies has been observed the linkage between HBV genotype B and HCCto be more strongly at an earlier stage but this observation hasn't been confirmed in other studies.[50] In Saudi Arabia, where genotype D is predominant, HBV associated liver cancer ranks as the second most common cancer among men, pointing to a significant correlation between HBV genotype D and liver cancer.[51] Various factors such as age, male gender, frequent severe acute exacerbations, nucleotide mutation frequency, and HBV reactivation after HBeAg sero-conversion increase the risk of advanced liver diseases in CHB patients.[52]

A study conducted by C Fernandes da Silva *et al*. highlighted the uncertainty over which genotypes and subgenotypes pose the greatest risk for liver cancer and cirrhosis; however, his study suggested that HBV/C presents a greater risk.[53] The A2 subgenotype is often linked with high viral loads, leading to acute infection via horizontal transmission, while chronic and occult infections are due to subgenotypes D1 and D3 respectively.[11,54] Yen–Hsuan Ni *et al*. demonstrated in their study that genotype B accounts for over 70% of chronic HBV infections in Taiwan, with delayed HBeAg sero-conversion noted in those with HBV genotype C.[55] Further changes and mixtures of genotypes appear only in individuals who experienced HBeAg sero-conversion during childhood HBV chronic infection. Genotype B remains predominant among the pediatric age group, making up the majority of HBsAg carrier children.[56]

8. Conclusion

The HBV genotypes and its variants may be used to predict the progression of the liver disease, which will help clinicians in developing effective therapeutic strategies and customize antiviral treatment. This study highlights genetic changes over the time and geographical location versus different geographical distributions of genotypes and sub-genotypes, which play pivotal role in disease progression, helping to devise necessary preventive measures to mitigate the onset of new infections and the spread of emerging genotypes across the globe and in India.

The emergence of genotypes or subgenotypes and its significant mutation plays a critical role in determining early clinical outcomes in different geographical areas. Delayed HBeAg sero-conversion was observed in patients with genotypes C and D in comparison to patients infected with genotypes A and B. Furthermore, those with C and D genotypes are more likely to experience worse clinical outcomes due to the quick progression of the disease and sometimes it may lead to HCC. In contrast to individual with genotypes C and D, those with genotypes A and B often respond therapies based on interferon. The efficacy of nucleotide analogue treatments and HBV genotype do not significantly correlate.

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None.

10. Conflict of Interest

None.

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