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Occult Hepatitis B infection (OBI) in Indonesia: A Systematic Review

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Abstract

Hepatitis B Virus (HBV) infection remains a significant global health concern, with various genotypes exhibiting distinct clinical characteristics. Occult hepatitis B infection (OBI) is a latent form of HBV infection that is difficult to detect and poses a risk of transmission, particularly among high-risk populations such as blood donors, hemodialysis patients, and kidney transplant recipients. In Indonesia, studies on HBV genotype diversity and OBI prevalence remain limited, highlighting the need for a systematic analysis better to understand genotype distribution and its implications for public health. This systematic review was conducted using the PRISMA guidelines. Literature searches were performed on Google Scholar, Springer, ResearchGate, ScienceDirect, and PubMed using keywords related to OBI, HBV genotypes, and the Indonesian population. Studies that met the inclusion criteria were analyzed to assess genotype distribution and OBI prevalence. Among 352 screened articles, 35 studies met inclusion criteria. Genotypes B and C were identified as predominant HBV strains, with regional distribution variations. The highest OBI prevalence was recorded in eastern Indonesia (13.03%), followed by central (4.31%) and western (3.36%) regions. Nested PCR was the primary detection method for OBI. The predominance of genotype C in eastern Indonesia may contribute to higher OBI prevalence, emphasizing the need for region-specific diagnostic and management strategies. Further research is necessary to elucidate the association between HBV genotypes and clinical outcomes in OBI patients.

Keywords: Occult hepatitis B infection, HBV, genotypes, Indonesia

Introduction

Hepatitis B virus (HBV) is a type of infection that is responsible for the inflammation of the liver. HBV is one of the major health problems in the world, and particularly due to its potential to cause serious liver complications such as cirrhosis and hepatocellular carcinoma. HBV counts 254 million people as victims in 2022, and the number of people infected in Indonesia stood at 17.5 million of all ages. This indicates Indonesia is one of the 10 major contributors to the health burden of hepatitis B infection (World Health Organization, 2024). After the introduction of the Hepatitis B vaccination program by Indonesia in 1997, though, the disease is still persistent; as seen in high-risk groups like patients undergoing dialysis, AIDS patients, diabetic patients, etc. Thus, understanding the way the infection occurred and the clinical effects of HBV are necessary for prevention and treatment strategies that are more effective.

Occult Hepatitis B Infection (OBI) is one of the critical aspects that require special attention in the study of hepatitis B. OBI causes various challenges related to clinical management and increases the risk of HBV transmission. This is because OBI causes the presence of HBV DNA to be undetectable through standard serological tests due to low or no levels of HBsAg antigen in the systemic circulation. This can occur in survivors of HBV infection who have recovered, but there is still HBV in the liver cells and mutates which causes evasion of conventional serological tests (Raouf et al., 2015). OBI in liver cells is in the form of covalently closed circular DNA (cccDNA), this form remains stable in hepatocyte cells and can contribute to the spread of DNA viruses to other hosts. Especially blood donors or liver organ donors from patients who have infectious viruses containing relaxed circular DNA (rcDNA) resulting from transcription from cccDNA to healthy people (Dong et al., 2018; Lin et al., 2016).

HBV has several genotypes with distinct geographic spread and health effects, including their role in liver diseases like cirrhosis and cancer (Purnamasari et al., 2019). Scientists have identified at least 10 HBV genotypes labeled A through J (Liu et al., 2021). Knowing these genotypes helps tailor treatment plans and vaccines to the type common in each area. Indonesia is an archipelagic country that has a unique geography and consists of various ethnicities and cultures that are diverse, which can possibly affect the distribution of HBV genotypes. Therefore, the spread of OBI and genotypes across Indonesia plays a key role in managing HBV prevention and treatment. This systematic review article aims to give a snapshot of OBI and HBV genotype distribution in Indonesia hoping to boost public and healthcare workers' knowledge about HBV infection issues.

Methods

Literature search strategy

This systematic review has been registered in PROSPERO with the registration ID **CRD420251121245**. We used the following methodological approaches, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to find papers on OBI and HBV Genotypes that had been spreading across Indonesia (Moher et al., 2009; Mateo, 2020; Campbell et al., 2020). Different search engines such as Google Scholar, ResearchGate, ScienceDirect, and PubMed were employed to locate the data or literature. The method sought to find a suitable combination of keywords like Occult Hepatitis B Infection, HBV Genotype, Blood donors, Chronic Hepatitis B, Chronic Hepatitis B patients, Genotypes diversity of HBV, Kidney transplant, and Indonesia as well as other keywords that support the search for this systematic review, by combining search tools such as the use of AND and OR to optimize search results.

Inclusion and exclusion criteria

The inclusion criteria in this systematic review include articles that are original research results and can be fully accessed. The included studies must be conducted in populations originating from Indonesia. The population is made up of individuals who are concerned with the hepatitis B virus (HBV) infection, which include blood donors, patients with acute or chronic hepatitis B, patients with hepatocellular carcinoma (HCC) as well as patients who have undergone (are undergoing) hemodialysis and/or liver transplantation. Furthermore, apart from showing the data on Occult Hepatitis B Infection (OBI) prevalence, the articles should also reveal the characteristics of the study group, and the study subjects' geographic location or demographic distribution. Another issue to consider for eligibility is getting the survey subjects to be molecular-based, and that is done through the hepatitis B virus (HBV) DNA detection technique.

While, exclusion criteria included articles that did not examine patients with OBI or HBV genotypes in Indonesia. Articles that only relied on OBI detection through the presence of hepatitis B core antibodies (anti-HBcAb) or hepatitis B surface antigen (HBsAg) without further confirmation through HBV DNA detection were also excluded from the analysis in this systematic review

Data extraction

Data collected from selected articles include several important information that support the analysis of this systematic review. This information contains the level of the presence of Occult Hepatitis B Infection (OBI), the group of people being studied, and the demographic places of the patients used to depict the geographic spread of cases. Furthermore, there are other things that we can learn from the data like the diagnostic methods that were in use in each study of the presence of hepatitis B virus (HBV) DNA, which is an OBI diagnosis indicator. The method of article selection and screening was intentionally and openly described following the PRISMA flow diagram, which is demonstrated in Figure 1. Meta-analysis was not conducted due to the high heterogeneity in study designs, populations, and outcome measurements across the included studies.

Ethical clearance

Since this study is a systematic review, no separate ethical approval submission is required for the conduct of this review.

Quality Assessment and Risk of Bias

Screening was conducted independently by three authors, who cross-checked each other's work. This process aimed to minimize bias in the article selection process. The screening was performed on the title, abstract, and full text of each study based on pre-established inclusion and exclusion criteria. In cases where discrepancies in the screening results occurred, discussions were held among the authors to reach a consensus on the articles considered problematic. This approach was intended to maintain objectivity and minimize subjectivity in the study inclusion process. The methodological evaluation of each article meeting the inclusion criteria from the initial screening was conducted using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Prevalence Studies. Selected articles were those with a satisfactory to good methodological evaluation, considering factors such as sample selection, clarity of the study population, and the appropriateness of the diagnostic methods employed.

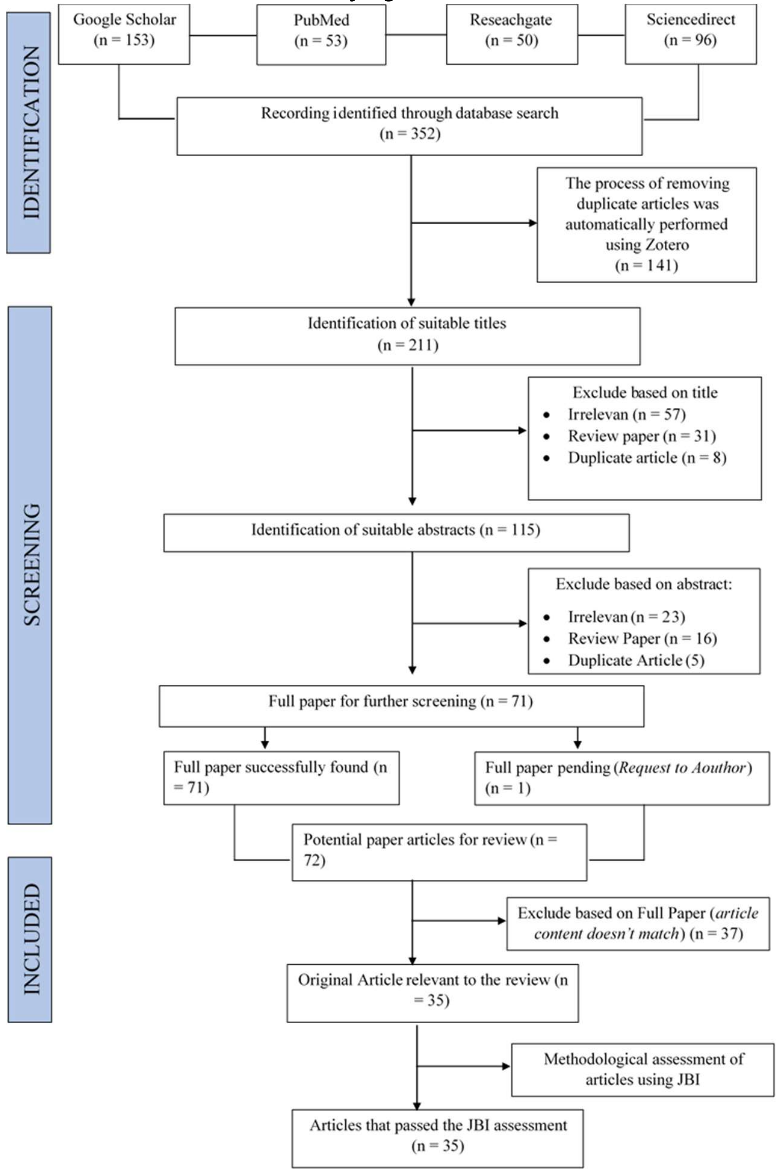

Figure 1. PRISMA *flowchart of screening articles*

Results

Our identification stage successfully collected 352 scientific articles from various pages used. The next stage is screening in accordance with the inclusion and exclusion criteria that have been set in the method in this systematic review. The analysis using the JBI Critical Appraisal Checklist for the 35 selected articles revealed that the methodologies employed in each article were rated as satisfactory to good. This was demonstrated by the fact that at least 5 out of 8 questions showed positive results. In the final stage, we found 35 relevant scientific articles that met the standards of critical assessment and were then synthesized as shown in Tables 1 and 2. Accumulative calculations were carried out based on the sample origin of all research articles based on Presidential Decree (Keppres) Number 41 of 1987 with the division of western Indonesia, central Indonesia, and eastern Indonesia (Figure 2) (Pembagian Wilayah Republik Indonesia Menjadi 3 (Tiga) Wilayah Waktu, 1987).

Eastern Indonesia showed the highest prevalence of OBI, followed by middle Indonesia, while western Indonesia had the lowest prevalence (Table 1). This condition is based on the prevalence value obtained through observations using the nested PCR method. Because OBI DNA analysis in central and eastern Indonesia did not use real-time PCR or conventional PCR methods, the data cannot be directly compared with western Indonesia. However, based on data from western Indonesia, the prevalence observed using real-time PCR and PCR methods showed lower figures (Table 1).

The genotype distribution in the various regions of Indonesia, according to the percentage, indicates that genotype B is the major one in the western and central regions, with a frequency of about 80%. On the other hand, in the eastern region of Indonesia, the prevalence of genotype C is over 70%. Additionally, to genotypes B and C, genotypes A and D were also detected but in very small numbers, namely with a prevalence of less than 1% throughout Indonesia. The exception occurred in the eastern region, where genotype D was found with a prevalence of more than 4% (Table 2).

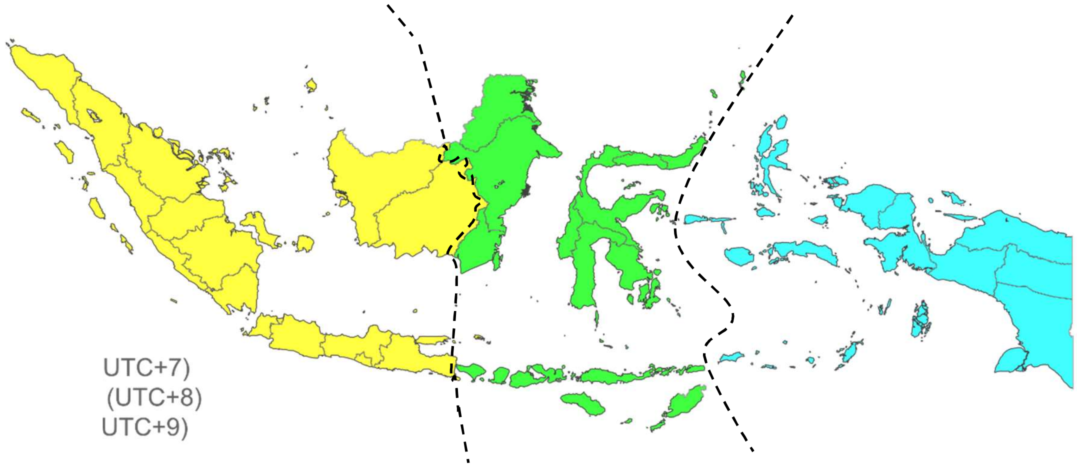

Figure 2. The division of sample origin regions refers to Presidential Decree (Keppres) Number 41 of 1987, namely as follows: (1) The western region of Indonesia (yellow) includes all provinces and cities on the island of Sumatra, all provinces and cities on the island of Java, and part of the Kalimantan region (West Kalimantan and Central Kalimantan); (2) The central region of Indonesia (green) includes part of the Kalimantan region (South Kalimantan, East Kalimantan, and North Kalimantan), all provinces and cities on the islands of Bali, Nusa Tenggara, and Sulawesi; (3) The eastern region of Indonesia (blue) includes all provinces and cities on the islands of Maluku and Papua (Wikipedia, 2025)

Table 1. Prevalence of OBI in Indonesia

Geographic Area	Number of Samples	Characteristics of population		Prevalence of OBI (%) Method of Detection			Reference
		Age range (Years)	Gender (Male/Female)	*Real Time* PCR	*Nested* PCR	PCR	
Western Indonesia	2145	1 – 80	1231/534 (1765 from 2145 identified)	0.98	3.36	0.14	(Widjaja et al., 1996; Mardian et al., 2017; Gunardi et al., 2017; Purwono et al., 2016; Meilani et al., 2016; Hadikusumo et al., 2016; Thedja et al., 2010; Rinonce et al., 2013; Utsumi et al., 2010)
Central Indonesia	534	1 - 41	193/312 (508 from 534 identified)	-	4.31	-	(Purwono et al., 2016; Darmawan et al., 2015; Purnamasari et al., 2019)
Eastern Indonesia	376	17 - 25	138/238 (376 from 376 identified)	-	13.03	-	(Ie et al., 2015)

Table 2. Distribution of HBV genotypes in Indonesia

Geographic Area	Number of Positive HBV DNA Samples	Genotype (%)				Reference
		A	B	C	D	
Western Indonesia	1221	0.41	80.51	19.00	0.08	(Mardian et al., 2017; Gunardi et al., 2017; Purwono et al., 2016; Meilani et al., 2016; Hadikusumo et al., 2016; Rinonce et al., 2013; Utsumi et al., 2010; Thedja et al., 2010; Utsumi et al., 2016; Widasari et al., 2014; Mulyanto et al., 2009; Putri et al., 2019; Utama et al., 2011; Wasityastuti et al., 2016; Lusida et al., 2003; Turyadi et al., 2013; Supiana Dian Nurtjahyani & Retno Handajani, 2021; Juniastuti et al., 2013; L. N. Yamani et al., 2015; Wungu et al., 2019; Ave et al., 2022; Juniastuti et al., 2010; Prasetyo et al., 2018; Utama et al., 2011)
Central Indonesia	968	0.31	79.65	19.63	0.41	(Purwono et al., 2016; L. Yamani et al., 2019; Darmawan et al., 2015; Mulyanto et al., 2009; Wahyuni et al., 2019; Utama et al., 2009; Thedja et al., 2011; Purnamasari et al., 2019; Mulyanto et al., 2010)
Eastern Indonesia	323	0.62	23.84	71.21	4.33	(Mulyanto et al., 2009; Juniastuti et al., 2011; Thedja et al., 2011; Lusida et al., 2008; Nurainy et al., 2008)

Discussion

The results of the systematic review show that the distribution of OBI prevalence in Indonesia shows striking variations between regions in Indonesia. The prevalence of OBI in Western Indonesia according to the data gathered and the detection method used ranged from 0.14% to 3.36% with a total sample size of 2145. Meanwhile, the central region of Indonesia registered an OBI prevalence of 4.31% out of 534 samples, indicating a heavy OBI burden in this area. Only in the eastern region of Indonesia, the highest OBI prevalence of 13.03% was identified from 376 samples and thus, there might be a hidden public health problem that has not been broadly revealed in this region. This unevenness in the prevalence can be considered as a demonstration of OBI transmission complexity and the necessity of clinical and research settings to use highly sensitive diagnostic method.

For the three regional groups, the nested PCR method is commonly used and records more OBI prevalence than the real-time PCR and conventional PCR methods. These results are consistent with previous findings showing that the detection method used has a major influence on the estimation of OBI prevalence. The nested PCR method is the main choice in OBI detection because of its ability to detect HBV DNA at very low levels, which are often undetectable by conventional PCR or qPCR (Raimondo et al., 2019; Liu et al., 2021). This is due to the two-stage amplification mechanism used in nested PCR, where the second primer will amplify the product of the first amplification, thereby increasing the sensitivity and specificity of detection. In addition, nested PCR can minimize the risk of non-specific amplification that can occur in conventional PCR, as well as overcome the limitations of qPCR which sometimes fails to detect very small amounts of DNA due to the detection threshold of the device or the presence of inhibitors in the sample (Raimondo et al., 2019). Therefore, nested PCR is a highly recommended method in OBI surveillance, especially in populations with low levels of viremia.

This high number is likely caused by several factors, such as the high level of endemicity of HBV infection in eastern Indonesia (Yano et al., 2015; Kemenkes RI, 2022). Limited access to health services and less than optimal coverage of birth dose HBV vaccination (World Health Organization, 2023; Kementerian Kesehatan Republik Indonesia, 2023). The presence of genetic factors in a population may also contribute to the tendency to maintain infection in the form of OBI (Zhang et al., 2019). This condition risks increasing the incidence of latent transmission, especially in risk populations such as immunocompromised patients or blood transfusion recipients. Additionally, low coverage of molecular-based screening can also cause OBI cases to go undetected optimally. However, further research is needed to specifically identify these risk factors. These findings underline the urgency of implementing a broader and standardized OBI detection strategy throughout Indonesia, especially in areas with high prevalence. Furthermore, the distribution of HBV genotypes also influences the emergence of OBI, where more aggressive genotypes have the potential to increase the risk of long-term complications and strengthen the persistence of infection. (6) Therefore, knowing the HBV genotype is an important step in reducing the risk of OBI.

The identification of the high rate of OBI in eastern Indonesia is consistent with the spread of hepatitis B virus (HBV) genotypes in that part of the country. The HBV distribution profile in Indonesia mainly comprises genotypes B and C, with the patterns of each region, which are western, central, and eastern Indonesia, being different. Genotype B is widespread in the western and central areas, and previously it has been the most frequent genotype in the Southeast Asia region, including Indonesia. Genotype B common in Asia including Indonesia, has a connection to earlier HBeAg seroconversion, milder histological activity, and better results with interferon therapy compared to other genotypes. It also has a link to a lower chance of cirrhosis and hepatocellular carcinoma (HCC) developing (Hayashi et al., 2021). On the other hand eastern Indonesia shows the highest rates of genotype C compared to genotype B. This points to differences in the virus's genetic clusters in the region. This variation is suggested to have been affected by ethnogenetic factors and the history of population migration in eastern Indonesia. Genotype C is an aggressive form of the disease, including slow or no HBeAg seroconversion rates, high viral loads, and higher frequencies of basal promoter mutations T1762/A1764 and pre-S deletion, which significantly increase the risk of HCC (Lin & Kao, 2015; Hayashi et al., 2021). The fact that the prevalence of genotype C is higher may also be one of the causes of the high OBI rate in eastern Indonesia, as the characteristics of this genotype tend to support the perseverance of the virus in the body and potentially cause hidden infections.

Concerning genotypes B and C, which are positioned at the top of the Indonesian genotype chain, this country is also the birthplace of some studies that revealed the existence of minor genotypes, namely genotypes A and D, which have been detected in a very small number of particular geographical regions. Although genotypes A and D are not frequently seen, it is important to note that the presence of those genotypes implies the potential of the virus invasion from other places, which might be due to the movement of people or cross-country transmission. Genotypes A and D themselves are known to have a wide global distribution, covering Sub-Saharan Africa, Europe, Central Asia, and countries in the Mediterranean region (Lin & Kao, 2015). Genotype A has a high level of chronicity after acute infection, although the response to interferon therapy is better than other genotypes, then genotype A has a higher rate of HBeAg and HBsAg seroconversion compared to genotypes C and D (Tian & Jia, 2016; Chien et al., 2019). Meanwhile, genotype D shows a tendency for more severe disease progression compared to genotype A, with a slower rate of seroconversion and a high prevalence of BCP mutations, and a relatively low response to interferon therapy (Tian & Jia, 2016; Chien et al., 2019).

These genotype distribution differences will determine the optimal therapeutic interventions and HBV management policy tracks for Indonesia. The predominance of genotype C in the eastern part of Indonesia could probably be a sign of the requirement to start the early-stage detection campaign and to perform more aggressive disease management focused on the prevention of long-term complications that are possible to result from the late stage of the infection. At the same time, the unabated spread of genotype B in the west and the center very well proves that the vaccine, which has been extensively used in those regions, was and is still highly effective.

Conclusion

This systematic review shows how OBI rates and HBV genotypes differ across Indonesia. OBI is most common in eastern Indonesia (13.03%) then central (4.31%), and western (3.36%) areas. Genotype B is more common in western and central Indonesia, while genotype C dominates the east. Genotype C linked to long-lasting infection and low virus levels, might explain the high OBI rates in the East. These results highlight the need for diagnosis and treatment plans that consider location and genetics. These findings emphasize the importance of diagnostic and management strategies that consider geographic and genetic factors, as well as the need for increased molecular screening to reduce the risk of long-term complications. Therefore, Indonesia should focus on preventing and spotting OBI using a region-based approach to control hepatitis B.

Conflict of Interest

No potential competing interest was reported by the authors.

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Author contribution

The study was conceptualized and designed by TPV, KS, TNM, and FAF, who also supervised the research process and critically reviewed the manuscript. NSM conducted the literature search, performed study selection, data extraction, and drafted the initial manuscript, including the section on quality assessment and risk of bias. TNM and TPV provided expert input on the virological relevance of occult hepatitis B infection. LHS provided general oversight and clinical validation of the content. All authors read and approved the final version of the manuscript.

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