Review article

Occult B hepatitis infection

Running head: OBI

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Abstract

Occult B Hepatitis Infection (OBI) is a condition in which HBsAg tests are negative, but Hepatitis B virus (HBV) DNA is detectable in the liver, with or without low levels of HBV DNA in the blood (<200 IU/mL). The Hepatitis B

surface antigen (HBsAg) negative status in OBI may result from the absence or low production of HBsAg due to immune system defense mechanisms or mutations in the S genome of HBV DNA, which make HBsAg undetectable. The gold standard for diagnosing OBI is testing for HBV DNA from liver tissue, with an alternative method being HBV DNA testing from serum. Patients with OBI may be at risk of transmitting HBV to others through blood transfusions or organ transplants. Reactivation may occur, especially in OBI patients who are immunocompromised or undergoing immunosuppressive therapy. Antiviral prophylaxis may be considered for OBI patients at risk of reactivation. Additionally, OBI patients also carry a risk of developing hepatocellular carcinoma (HCC), similar to those with non-occult hepatitis B infection. Antiviral therapy for OBI is generally not required unless the case represents false OBI due to HBsAg mutation.

Keywords: Hepatitis B surface antigen; hepatitis B virus; occult B hepatitis infection.

Introduction

Hepatitis B is a disease caused by the Hepatitis B virus (HBV). It is a major global health issue, with 360 million people chronically infected worldwide. This disease has a wide spectrum, ranging from occult infection to fulminant hepatitis with cirrhosis and hepatocellular carcinoma (HCC).[1] In 2019, the World Health Organization (WHO) reported that 296 million people were living with HBV infection, with 1.5 million new cases and 820,000 deaths annually due to complications such as cirrhosis and HCC.[2] The majority of HBV-related deaths occurred in Asia (74%). In Indonesia, the prevalence of HBV infection was 7.1%, based on data from Riskesdas in 2013. Occult B Hepatitis Infection (OBI) plays a significant role in Hepatitis B cases in Indonesia.[3]

OBI is a condition in which Hepatitis B surface antigen (HBsAg) is negative, but viral replication is present in the liver, with low levels of HBV DNA (<200 IU/mL). Although HBV DNA is detected at low levels, patients with OBI can still transmit the virus.[4] The global prevalence of OBI among blood donors who tested negative for HBsAg was found to be 6.2% in a sample of 6,757,391 blood donors. Southeast Asia showed a higher prevalence of 16.73% among 2,243 blood donors.[5] In Indonesia, OBI prevalence was 8.1% among 309 blood donors with negative HBsAg. This variation is attributed to differences in the endemicity of HBV infection.[1]

OBI was first reported in the 1970s in a post-transfusion patient who developed HBV infection despite receiving HBsAg-negative blood. In 1999, HBV DNA was detected in a liver biopsy from a patient with chronic liver disease who tested negative for HBsAg. Since then, the term OBI has appeared in numerous medical publications. The primary concern regarding OBI is its clinical impact. Blood or liver transfusion from OBI donors places recipients at risk of Hepatitis B infection, similar to transfusions from donors who test positive for HBsAg. OBI can reactivate into full-blown Hepatitis B infection and progress to cirrhosis and HCC, particularly in immunosuppressed patients.[4] This paper explores the virology of HBV and the definition of OBI, disease progression, diagnosis, transmission risk, reactivation, complications, and treatment.

Definition of OBI

OBI is defined as the presence of competent HBV capable of replication, indicated by the detection of HBV DNA in the liver with or without the presence of HBV DNA in the patient's blood, along with a negative HBsAg result using currently available HBsAg tests. The HBV DNA detected in OBI is typically intermittent and at low levels, usually less than 200 IU/mL or 1,000 viral copies/mL. This characteristic distinguishes OBI from overt Hepatitis B infection, in which a positive HBsAg result is accompanied by a high viral load.

OBI can be classified based on antibody profiles against HBV into seropositive and seronegative OBI. In seropositive OBI, antibodies against the HBV core (anti-HBc) are present. Approximately 80% of OBI cases are seropositive. In contrast, anti-HBc is absent in seronegative OBI. The undetectable HBsAg in OBI may result from HBsAg levels being too low to be detected, failure of HBsAg production, or mutations in HBsAg itself. Mutations in

HBsAg cause “false OBI,” in which HBsAg tests are negative despite high levels of HBV DNA due to active viral replication.[4,6]

Hepatitis B Virology

Hepatitis B virus is an enveloped virus of small size (42–50 nm) containing partially double-stranded circular DNA. The viral envelope consists of lipids and HBsAg proteins on the surface, which vary in size (small, medium, and large). The nucleocapsid has an icosahedral shape with 90–120 Hepatitis B core (HBc) proteins or Hepatitis B core antigen (HBcAg). Inside the nucleocapsid are the HBV genome and viral polymerase. Hepatitis B e-antigen (HBeAg) is a product generated during the translation process and serves as a marker of viral replication.[7,8]

The genomic structure of HBV consists of the S, P, C, and X genes, which overlap with each other. The S gene, comprising the pre-S1, pre-S2, and S open reading frames (ORF), is responsible for the production of HBsAg. The P gene, the longest gene, encodes the viral polymerase. The C gene consists of the pre-C ORF and C ORF, which contribute to the formation of the HBc protein and the secretion of HBeAg. The X gene encodes the HBx protein, a non-structural protein of HBV.

Disease Progression

The absence of HBsAg in OBI is caused by several mechanisms, including recovery from acute and chronic Hepatitis B infections, the absence of Hepatitis B infection markers in early infection (as seen in seronegative OBI), and mutations in the HBV S variant. A positive result for HBsAg and IgM antibodies against HBcAg (anti-HBc) can be found during acute Hepatitis B infection. The persistence of HBsAg for more than six months indicates chronic infection. Recovery from Hepatitis B infection may result in HBsAg becoming negative. In addition to anti-HBc, anti-HBs may also be detected as a marker of prior acute infection. However, it should be noted that in some cases of Hepatitis B infection, HBsAg may disappear spontaneously without any treatment.[1,6,9]

Seronegative OBI may result from the loss of anti-HBc or anti-HBs during disease progression or from the complete absence of serological markers except for HBV DNA.[6,10] A summary of OBI progression is shown in Figure 1.

The persistence of HBV DNA in the hepatocytes of OBI patients is caused by the suppression of viral replication and protein expression by the host immune system. However, the immune system cannot completely eradicate the virus from infected hepatocytes. Suppression of HBV DNA transcription and replication results in low plasma HBV DNA levels. Nevertheless, the covalently closed circular DNA (cccDNA) of HBV in OBI remains capable of viral replication. Factors involved in suppressing HBV replication in OBI include the host immune response, coinfection, and epigenetic mechanisms. The immune system limits antigen expression through efficient T-cell responses. Coinfection with other viruses, such as Hepatitis C, can inhibit HBV replication. Epigenetic modification, such as CpG methylation of cccDNA, can enhance histone methylation of cccDNA. This alteration modifies transcriptional activity and reduces HBV mRNA formation, ultimately resulting in decreased HBV protein synthesis.[4,6,11]

Overt HBV infection begins with the presence of circulating virus in the bloodstream. The HBs protein on the viral surface initially binds to heparan sulfate proteoglycan (HSPG) with low affinity. High-affinity binding occurs between the HBs protein and sodium taurocholate co-transporting polypeptide (NTCP), forming the HBV–NTCP complex. The HBV–NTCP complex then enters hepatocytes via endocytosis. Inside the hepatocyte, the relaxed circular DNA (rcDNA) is released into the nucleus, where it is converted into cccDNA or integrated into host DNA. The cccDNA is transcribed into HBV mRNA, which is then translated into viral proteins. The viral proteins, including HBsAg, are released into circulation and become detectable by diagnostic tests.[6,11,12]

In OBI, the infection starts with HBV nucleocapsids already present within hepatocytes, which then enter the nucleus to form rcDNA. The rcDNA is converted into cccDNA. The cccDNA undergoes methylation, specifically CpG methylation by DNA methyltransferase (DNMT), which prevents its expression. DNA methylation leads to the binding of DNA methyl-binding proteins (DNA MBP) to the methylated DNA, which then recruits transcriptional corepressors such as histone deacetylase (HDAC). Elevated levels of HDAC, along with histone methyltransferase (HMT) and Sirtuin 1 (Sirt1), enhance histone methylation, further suppressing cccDNA expression. This process

results in HBx-mutated HBV, which produces less HBV mRNA. In HBx-mutated HBV, the increase in apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3 (APOBEC3) inhibits heterogeneous nuclear ribonucleoprotein K (hnRNPK), further decreasing HBV mRNA synthesis. The reduced HBV mRNA leads to the production of fewer HBV proteins. Additionally, increased microRNA (miRNA) activity also inhibits HBV protein synthesis, further decreasing the amount of protein formed.[6,11,12]

There are some cases in which HBsAg may not be detected by assays due to mutations. These conditions are referred to as "false OBI." HBV DNA detected in false OBI cases can be high—comparable to that in overt Hepatitis B infection—but with negative HBsAg due to mutation. HBV with mutations in the S gene, particularly in the pre-S region, is referred to as the S variant. The S variant HBV can form modified HBsAg with low antigenicity. This modified HBsAg in HBV S variants cannot be detected by some commercial HBsAg tests, although cases of OBI due to S gene mutations are rare. S gene mutations most frequently occur in the α determinant sequence region. The substitution of glycine with arginine at position 145 (G145R) is the most frequently reported mutation. This mutation was first identified by Carman in 1990 in an infant born to a carrier mother who had been vaccinated and given immunoglobulin therapy since birth, yet the baby developed HBV infection.[13] A study by Araujo et al.[14] in Brazil, which sequenced DNA from OBI patients, found S mutations in the E164D, I195M, P217L, and P120S regions, with E164D and P120S located in the α determinant sequence region.

Diagnosis of OBI

The diagnosis of OBI is based on the detection of HBV DNA from a patient's liver biopsy along with a negative HBsAg result. The gold standard for diagnosing OBI is testing for HBV DNA in liver biopsy samples; however, this test has not yet been standardized or validated. Other tests that may be performed include testing for HBV DNA in blood samples, as well as HBsAg, anti-HBc, and anti-HBs.[6,15] The diagnostic pathway for suspected OBI is illustrated in Figure 2.

1. HBV DNA

The recommended method for HBV DNA testing in liver tissue samples is nested PCR (Polymerase Chain Reaction) or real-time PCR, which amplifies at least three regions of the viral genome.[4,6] A study by Faria et al.[16] compared nested PCR from liver biopsy using two protocols. Protocol 1 amplified four regions of the viral genome, while Protocol 2 amplified two regions to confirm the diagnosis of OBI in 104 HBsAg-negative patients with chronic liver disease. Protocol 1 demonstrated higher sensitivity in detecting HBV DNA (12.5%) compared to Protocol 2 (8.7%).

HBV DNA testing from blood samples is more commonly used than liver tissue testing due to the ease of obtaining blood samples, whereas liver biopsy is more invasive. However, HBV DNA found in liver tissue remains the gold standard for diagnosing OBI. This is supported by a study conducted by Wang et al.[15], which compared HBV DNA testing from liver tissue. Table 1 presents the results of three studies compiled by Wang et al.[15], showing that HBV DNA detection in liver tissue had higher sensitivity for OBI than detection in blood samples.[17-19] This finding is also supported by another study from Cakal et al.[20], which assessed the presence of OBI in 59 patients with chronic Hepatitis C and negative HBsAg. In that study, 16 patients with negative HBsAg had positive HBV DNA in their liver tissue, but none of these patients had positive serum HBV DNA.[20]

HBV DNA detected in the blood of OBI patients is typically at low levels, usually <200 IU/mL, and 80–90% of cases show levels <20 IU/mL. Meanwhile, the detection limit of current commercial HBV DNA tests is 10–20 IU/mL. HBV DNA in the blood is also detected intermittently, making it harder to identify. Therefore, it is recommended that blood HBV DNA testing be performed more than once, using a sample volume of at least 1 mL. HBV DNA testing is crucial for distinguishing between true occult infection and "false OBI."[15,21]

2. HBsAg

The detection limit for HBsAg testing ranges from 0.005–0.05 IU/mL (Table 2). HBsAg testing with a minimum detection limit of 0.005 IU/mL can detect HBsAg in 5–48% of patients who were previously HBsAg-

negative.[4,11,22–24] Although current commercial HBsAg tests can detect small amounts of HBsAg, they still have limited ability to identify HBsAg S variants. Therefore, the use of anti-HBs conjugates targeting multiple epitopes of HBsAg improves the ability to detect HBV S variants.[4,6]

Kuhns et al.[24] found in their study that the latest prototype HBsAG test with a lower detection limit could detect OBI in 3 of 7 HBV samples carrying HBsAg escape mutations. In the remaining four samples that were not detected, it was likely due to HBsAg levels being below the detection threshold rather than due to the mutations themselves. These mutations were detectable in other studies using HBsAg tests with the same prototype.[24,25]

3. Anti-HBc

The anti-HBc test can serve as an alternative for diagnosing OBI in organ or blood donors, patients who are about to receive immunosuppressive therapy, or for use in epidemiological studies. This test is particularly useful when liver tissue is unavailable and access to HBV DNA testing is limited or delayed. A negative result for HBV DNA in the blood on the first test does not rule out the diagnosis of OBI; therefore, additional anti-HBc testing is necessary. However, a negative anti-HBc result also does not exclude OBI, as seronegative OBI cases exist.[6,11]

This is supported by a study conducted by Cakal et al.[20], which found that 18.71% of OBI patients were seronegative for both anti-HBc and anti-HBs. A positive anti-HBc result indicates past or current HBV infection; however, confirming the diagnosis of OBI still requires HBV DNA testing.[6,11]

4. Anti-HBs

Anti-HBs is a protective marker against HBsAg infection. Its presence can neutralize the virus and resolve OBI, thereby reducing the likelihood of OBI.[11] This was demonstrated in a study by Cai et al.[26], which showed that the incidence of OBI was higher in patients who were anti-HBs negative, as shown in Table 3. The data in Table 3 highlight the role of anti-HBs in neutralizing HBV infection, resulting in a lower OBI incidence in individuals who are anti-HBs positive.

5. HBeAg

HBeAg is a circulating HBV antigen found in patient serum. Although HBeAg is not required for replication, its presence indicates active viral replication. Therefore, a negative HBeAg result does not rule out the diagnosis of OBI. A positive HBeAg in OBI cases contradicts the typically negative HBsAg result.[7] In a case report by Han et al.[27], two patients were HBsAg negative but both HBV DNA and HBeAg were positive. They were later found to have HBV escape mutations.

6. HBcrAg

Hepatitis B core-related antigen (HBcrAg) consists of HBcAg, HBeAg, and the 22 kDa precore protein (p22cr). According to the European Association for the Study of the Liver[28] and a systematic review by Mak et al.[29] (Table 4), HBcrAg reflects intrahepatic DNA and cccDNA. This is also supported by a case report by Yokoyama et al.[30] in Japan. In that case, a patient who was negative for HBsAg, HBeAg, anti-HBc, anti-HBs, and anti-HBe, and had undetectable HBV DNA (<1300 IU/mL), was found to have elevated HBcrAg levels and experienced recurrence of hepatocellular carcinoma (HCC).

The use of HBcrAg to detect HCC complications in patients with negative HBsAg is also supported by a study by Hsieh et al.[31], which found that positive HBcrAg significantly increased the risk of developing HCC compared to patients with negative HBcrAg (OR 9.3 [3.3–26.4]; $p<0.001$). This demonstrates that HBcrAg can help monitor the progression of OBI toward HCC. However, since HBcrAg testing is relatively new and studies on its correlation are still limited, it cannot yet be routinely used to diagnose OBI.

Transmission of OBI

In OBI, cccDNA can persist in hepatocytes for a long time, even when HBsAg is not detectable. Various studies related to blood donation from patients with OBI have shown that it can lead to Hepatitis B infection in the recipient. Blood product screening to prevent the transmission of HBV infection through transfusion usually relies on HBsAg testing. However, HBV infection from an OBI donor will not be detected using this parameter alone. Therefore, some blood transfusion units implement PCR screening for HBV DNA using a pooling system to reduce costs. Six to fifty HBsAg-negative donor samples are collected, pooled, and tested for HBV DNA by PCR. If a positive result is found, further HBV DNA testing is conducted on each sample to identify the positive one.[32]

The transmission rate of OBI through blood products is highest with fresh frozen plasma (FFP) and thrombocyte concentrate (TC), at 85% and 51%, respectively. Blood products such as packed red cells (PRC) have a lower transmission rate, at 24%.[33] This is because FFP and TC contain more plasma volume than PRC, resulting in a higher number of virions being transfused. This is supported by a case report by Candotti et al.[34], which identified nine cases of HBV infection in recipients from OBI donors. Seven of these cases involved FFP recipients, while two involved PRC recipients.

The risk of HBV transmission from OBI patients can also occur through organ transplantation. Liver transplant recipients are at a similar risk of HBV infection whether the organ donor has overt HBV infection or OBI.[4] A systematic review conducted by Cholongitas et al.[35] found that the incidence of HBV transmission from OBI donors was highest in recipients who had never been infected with HBV. The administration of prophylaxis, such as lamivudine, significantly reduced the proportion of recipients who developed HBV infection. The most significant reduction was observed in recipients who were HBV naïve, as shown in Table 5. Table 5 also highlights the protective effect of anti-HBs, with populations positive for anti-HBs showing a lower incidence of HBV infection compared to those who were anti-HBs negative.

Reactivation and Complications of OBI

Patients with OBI are at risk of reactivation. The reactivation of HBV in OBI patients is defined as seroconversion to HBsAg positivity or an increase in serum HBV DNA by at least 1 log above the lower detection limit in patients who were previously undetectable, or a 1-log increase in those who previously had low HBV DNA levels. Reactivation typically occurs in patients receiving chemotherapy or immunosuppressive therapy. Approximately 40% of OBI patients experience HBV reactivation during immunosuppressive treatment, with the highest risk observed in those receiving anti-CD20 therapy.

HBV reactivation can also occur in patients with immunodeficiency due to HIV infection. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommend that HIV patients undergo HBV DNA testing and Hepatitis B serology to detect potential OBI and assess the risk of reactivation. Antiviral prophylaxis, such as nucleotide analogs, may be given to OBI patients who are at risk of HBV reactivation. Patients considered at low risk do not require prophylaxis but should be closely monitored.[6,36]

OBI patients are also at risk of progressing to hepatocellular carcinoma (HCC), particularly those with chronic Hepatitis B. A study by Mak et al.[11] found that 60–70% of patients with HCC of unknown etiology in Asia and Europe had OBI in their liver tissue. Furthermore, among 82 patients with cirrhosis of unknown cause who had OBI, 100% developed HCC within 5.8 years, while cirrhosis patients without OBI had only a 17.6% risk of developing HCC within 10 years.

Co-infection of OBI with Hepatitis C virus (HCV) further increases the risk of developing HCC. This co-infection leads to more severe liver damage compared to OBI without HCV co-infection.[4,7,11]

The presence of HBV DNA in OBI patients contributes to HCC progression because HBV DNA is proto-oncogenic within hepatocytes. HBV can integrate into the host genome and produce proteins with carcinogenic properties, such as the HBx protein, and also induce liver inflammation. The integration of HBV into the host genome disrupts the cell cycle and promotes tumor progression. The HBx protein, a non-structural protein of HBV, can regulate the cell

cycle, leading to dysregulation. This dysregulation causes mitochondrial dysfunction and uncontrolled cell proliferation, which supports HCC carcinogenesis.

Chronic liver inflammation can result in continuous hepatocellular damage, progressing to liver cirrhosis. In cases of OBI with HBsAg mutations, HBsAg becomes undetectable and may accumulate within cells. This accumulation induces endoplasmic reticulum stress, leading to DNA damage, genomic instability, and progression toward cancer.[4,7,11]

Treatment

Treatment of OBI patients currently does not require antiviral therapy. If the goal is to completely eliminate HBV from the hepatocytes of OBI patients, strategies involving the direct elimination of cccDNA in hepatocytes can be considered. One such approach includes gene-editing techniques, such as CRISPR/Cas9, which specifically target cccDNA.

In addition to cccDNA elimination, another potential strategy is to enhance T-cell responses to eliminate infected hepatocytes in the liver. However, this therapeutic approach still requires further research. Therefore, current OBI management focuses primarily on preventing reactivation, transmission, and complications such as HCC.

It is important to note that in cases of false OBI, where HBsAg has mutated and is undetectable with current HBsAg tests, treatment should follow the same approach as for non-occult HBV infection, including the administration of antiviral therapy. Suspicion of mutation is particularly supported by a reactive HBeAg, which indicates active viral replication.[6,11]

Prophylactic therapy, such as lamivudine, may be given to OBI patients at risk of reactivation, especially those with detectable serum HBV DNA, even in small amounts. Prophylactic therapy should be continued for up to six months after the end of immunosuppressive treatment, or for 12 months after therapies targeting B cells. Monitoring should include liver function tests, HBV DNA, and HBsAg every three months.[37–39]

Conclusion

It is important to consider OBI when HBsAg is found to be negative, especially in endemic areas. Patients with OBI are at risk of transmitting HBV infection through blood transfusion and organ transplantation. Reactivation may occur, particularly in patients with HIV or those receiving immunosuppressive therapy, leading to overt HBV infection. They are also at risk of developing hepatocellular carcinoma due to persistent HBV infection.

Reference

Reference

1. Thedja MD, Roni M, Harahap AR, Siregar NC, Muljono DH. Occult hepatitis B in blood donors in Indonesia: Altered antigenicity of the hepatitis B virus surface protein. Hepatol Int 2010;4(3):608-614.
2. Teo EK, Lok ASF. Epidemiology, transmission, and prevention of hepatitis B virus infection. UpToDate; 2024. Available at: https://www.uptodate.com/contents/epidemiology-transmission-and-prevention-of-hepatitis-b-virus-infection Accessed on Feb 23, 2024.
3. Muljono DH. Epidemiology of hepatitis B and C in republic of Indonesia. Euroasian J Hepatogastroenterol 2017;7(1):55-59.
4. Saitta C, Pollicino T, Raimondo G. Occult hepatitis B virus infection: an update. Viruses 2022;14(7):1504.

5. Takuissu GR, Kenmoe S, Atsama MA, Okobalemba EA, Mbaga DS, Ebogo-Belobo JT, et al. Global epidemiology of occult hepatitis B virus infections in blood donors, a systematic review and meta-analysis. PLoS One 2022;17(8):e0272920.
6. Raimondo G, Locarnini S, Pollicino T, Levrero M, Zoulim F, Lok AS, et al. Update of the statements on biology and clinical impact of occult hepatitis B virus infection. J Hepatol. 2019;71:397-408.
7. Chapus L, Martinez MG, Testoni B, Zoulim F. Molecular virology and life cycle of hepatitis B virus. In: Kao JH, editor. Hepatitis B virus and liver disease. Edisi 2. Springer: Singapore; 2021. p. 1-508.
8. Anand P, Singh S, Schelonka RL, Tekleab AM, Upadhyay A. Hepatitis B infections in neonates. Newborn 2022;1(4):368-375.
9. Almeida NAA, Paula VS. Occult Hepatitis B virus (HBV) infection and challenges for hepatitis elimination: a literature review. J Appl Microbiol 2022;132(3):1616-1635.
10. Gherlan GS. Occult hepatitis B — the result of the host immune response interaction with different genomic expressions of the virus. World J Clin Cases 2022;10(17):5518-5530.
11. Mak LY, Wong DKH, Pollicino T, Raimondo G, Hollinger FB, Yuen MF. Occult hepatitis B infection and hepatocellular carcinoma: epidemiology, virology, hepatocarcinogenesis and clinical significance. J Hepatol 2020;73(4):952-964.
12. He P, Zhang P, Fang Y, Han N, Yang W, Xia Z, et al. The role of HBV cccDNA in occult hepatitis B virus infection. Mol Cell Biochem 2023;478(10):2297-2307.
13. Lalana Garcés M, Ortiz Pastor O, Solé Enrech G, Guerra-Ruiz AR, Casals Mercadal G, Almería Lafuente A, et al. Control of occult hepatitis B virus infection. Adv Lab Med 2022;3(4):321-341.
14. Araújo S dos R, Malheiros AP, Sarmento VP, Nunes HM, Freitas PEB. Molecular investigation of occult hepatitis B virus infection in a reference center in Northern Brazil. Braz J Infect Dis 2022;26(3):102367.
15. Wang C, Xue R, Wang X, Xiao L, Xian J. High-sensitivity HBV DNA test for the diagnosis of occult HBV infection: commonly used but not reliable. Front Cell Infect Microbiol 2023;13:1186877.
16. Faria AC, Correa BHM, Faria LC, Vidigal PVT, Xavier MAP, Ferrari TCA. Occult hepatitis B virus infection in patients with chronic liver disease of different etiology in a Brazilian referral center: comparison of two different hepatitis B virus deoxyribonucleic acid amplification protocols: a cross-sectional study. Sao Paulo Med J 2022;141(3):e2022147.
17. Yuki N, Nagaoka T, Yamashiro M, Mochizuki K, Kaneko A, Yamamoto K, et al. Long-term histologic and virologic outcomes of acute self-limited hepatitis B. Hepatology 2003;37(5):1172-1179.
18. Komori M, Yuki N, Nagaoka T, Yamashiro M, Mochizuki K, Kaneko A, et al. Long-term clinical impact of occult hepatitis B virus infection in chronic hepatitis B patients. J Hepatol 2001;35(6):798-804.
19. Knöll A, Hartmann A, Hamoshi H, Weislmaier K, Jilg W. Serological pattern anti-HBc alone: characterization of 552 individuals and clinical significance. World J Gastroenterol 2006;12(8):255.
20. Cakal B, Cavus B, Atasoy A, Poda M, Bulakci M, Gulluoglu M, et al. What is the clinical impact of occult HBV infections and anti-HBc positivity in patients with chronic hepatitis C. Microbiol Immunol 2022;66(8):386-393.
21. Pollicino T, Raimondo G. Occult hepatitis B infectio. J Hepatol 2014;61(3):688-689.
22. Ozeki I, Nakajima T, Suii H, Tatsumi R, Yamaguchi M, Kimura M, et al. Analysis of hepatitis B surface antigen (HBsAg) using high-sensitivity HBsAg assays in hepatitis B virus carriers in whom HBsAg seroclearance was confirmed by conventional assays. Hepatol Res 2018;48(3):E263-E274.
23. Wong DKH, Chen C, Mak LY, Fung J, Seto WK, Yuen MF. Detection of the hepatitis B surface antigen in patients with occult hepatitis B by use of an assay with enhanced sensitivity. J Clin Microbiol 2022;60(2):e0220421.
24. Kuhns MC, Holzmayer V, McNamara AL, Sickinger E, Schultess J, Cloherty GA. Improved detection of early acute, late acute, and occult hepatitis B infections by an increased sensitivity HBsAg assay. J Clin Vir 2019;118:41-45.
25. Lou S, Taylor R, Pearce S, Kuhns M, Leary T. An ultra-sensitive Abbott ARCHITECT® assay for the detection of hepatitis B virus surface antigen (HBsAg). J Clin Vir 2018;105:18-25.
26. Cai J, Wu W, Wu J, Chen Z, Wu Z, Tang Y, et al. Prevalence and clinical characteristics of hepatitis B surface antigen-negative/hepatitis B core antibody-positive patients with detectable serum hepatitis B virus DNA. Ann Transl Med 2022;10(1):25.
27. Han Z, Liu Y, Pan J, Bi Y, Liu J, Zhou YH. Occult hepatitis B virus infection with positive hepatitis B e antigen. Clin Chim Acta 2015;438:266-268.

28. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370-398.
29. Mak LY, Wong DKH, Cheung KS, Seto WK, Lai CL, Yuen MF. Review article: hepatitis B core-related antigen (HBcrAg): an emerging marker for chronic hepatitis B virus infection. Aliment Pharmacol Ther 2018;47(1):43-54.
30. Yokoyama K, Yamauchi E, Uchida Y, Kitaguchi T, Fukuda H, Yamauchi R, et al. Hepatitis B virus core-related antigen is useful for surveillance of hepatocellular carcinoma recurrence in a patient with occult hepatitis B virus infection: case report. Clin Case Rep 2020;8(12):3032-3037.
31. Hsieh YC, Pan MH, Jeng WJ, Hu HH, Liu J, Mizokami M, et al. Serum HBcrAg and hepatocellular carcinoma in a taiwanese population seronegative for HBsAg and anti-HCV. Clin Gastroenterol Hepatol 2023;21(5):1303-1313.
32. Esposito A, Sabia C, Iannone C, Nicoletti GF, Sommese L, Napoli C. Occult Hepatitis infection in transfusion medicine: screening policy and assessment of current use of anti-HBc testing. Transfus Med Hemother 2017;44(4):263-272.
33. Candotti D, Boizeau L, Laperche S. Occult hepatitis B infection and transfusion-transmission risk. Transfus Clin Biol 2017;24(3):189-195.
34. Candotti D, Assennato SM, Laperche S, Allain JP, Levicnik-Stezinar S. Multiple HBV transfusion transmissions from undetected occult infections: revising the minimal infectious dose. Gut 2019;68(2):313-321.
35. Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: A systematic review. J Hepatol 2010;52(2):272-279.
36. Lee BT, Perumalswami PV. Diagnosis and management of occult hepatitis b infection. Curr Hepatol Rep 2020;19(4):354-361.
37. Raimondo G, Filomia R, Maimone S. Therapy of occult hepatitis b virus infection and prevention of reactivation. Intervirology. 2014;57(3-4):189-195.
38. Cendrero RMR, Castellano BC, Martín MVH, Parra MCC, González JG, Solís MAF, et al. When can it be useful to look for occult HBV in haemodialysis patients. Nefrología. 2020;40(2):115-119.
39. Lau G, Yu ML, Wong G, Thompson A, Ghazinian H, Hou JL, et al. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. Hepatol Int 2021;15(5):1031-1048.

Table 1. OBI incidence based on detected HBV DNA from liver tissue compared to blood[15]

Study	Country	Year	Sample size	OBI incidence	
				Liver tissue	Blood
Yuki et al.[17]	Japan	2003	13	100%	21%
Komori et al.[18]	Japan	2001	15	100%	13.3%
Knoll et al.[19]	Germany	2006	545	41%	8.1%

HBV: Hepatitis B virus; OBI: Occult B hepatitis infection.

Table 2. Lower limit detection of HBsAg test[11]

HBsAg test	Manufacturer	Lower limit detection (IU/mL)
Architect HBsAg QT	Abbott Laboratories	0.05
Elecsys HBsAg II	Roche Diagnostics	0.05
Liaison XL Murex HBsAg Quant	DiaSorin	0.03
Lumipulse HBsAg-Quant	Fujirebio, Inc.	0.005

Ultrahigh sensitive HISCL HBsAg	Sysmex Co, Ltd	0.0005

HBsAg: Hepatitis B surface antigen; HISCL: Highly sensitive chemiluminescent.

Table 3. Incidence of OBI based on HBV serology[26]

Anti-HBs	Anti- HBc	Anti-HBe	OBI incidence
+	+	-	1.87% (13/695)
-	+	-	3.73% (10/268)
+	+	+	6.27% (53/845)
-	+	+	15.61% (32/205)

HBs: Hepatitis B surface; HBc: Hepatitis B core; HBe: Hepatitis B e antigen; OBI: Occult B hepatitis infection.

Table 4. HBcrAg correlation with intrahepatic HBV DNA and cccDNA [29]

HBcrAg with HBV DNA		
Sample size	Correlation coefficient	p
93	0.7	<0.001
305	0.67	<0.0001
HBcrAg with cccDNA		
Sample size	Correlation coefficient	p
93	0.64	<0.001
138	0.7	<0.0001
31	0.482	<0.006

HBV: Hepatitis B virus; HBcrAg: Hepatitis B core-related antigen.

Table 5. Post-transplantation HBV infection incidence in recipient from HBsAg negative donor[35]

Recipient serology		HBV incidence without prophylaxis	HBV incidence without prophylaxis
Anti-HBs	Anti-HBc		
-	-	47.8%	12%[c]
-	+	13.1%[ab]	3.4%[c]
+	-	9.7%[a]	0%
+	+	1.4%[a]	N/A

[a]statistically significant compared with naive HBV (negative anti-HBs and anti- HBc) without prophylaxis
[b]statistically significant compared with positive anti-HBs and anti HBc without prophylaxis
[c]statistically significant compared with group without prophylaxis

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBs: Hepatitis B surface; HBc: Hepatitis B core

Figure Legends

Figure 1. Progression from hepatitis B infection to seropositive and seronegative OBI
Figure 2. Diagnosis pathway of OBI