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NARRATIVE REVIEW

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# Occult hepatitis B in Iranian blood donors, an overview of the challenges: A narrative review

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## Abstract

**Background:** Occult hepatitis B infection (OBI) is a transfusion-transmitted infection. Although, screening the hepatitis B virus among blood donors can play an important role in increasing the health of blood products, OBI screening in blood transfusion centers is still a challenge. This review study aimed to appraise the challenges of OBI screening and its associated do's and don'ts in blood transfusion centers.

**Methods:** In this review study, a search was conducted on the electronic databases of PubMed, Web of Science, Scopus, Ovid, Irandoc, and Magiran from January 1996 to December 2020. Also, cross-sectional studies that determined the prevalence of OBI or anti-HBc were included in the study. In addition, studies with incomplete data on the prevalence of OBI were excluded.

**Results:** The prevalence of OBI varies among Iranian blood donors. The rates reported by blood transfusion centers of Mashhad, Ahvaz, and Tehran were 0%, and Isfahan, Shiraz, and Kerman were 0.9%, 0.08%, and 2.36%, respectively. In areas with high prevalence of hepatitis B virus, OBI screening only by anti-HBc test led to the exemption of blood donors from donating blood. Avoiding OBI screening also effected the risk of virus transmission to blood recipients. Plasma products had a higher risk (85%) of virus transmission.

**Conclusions:** Determining an appropriate screening strategy based on prevalence status, the cost-effectiveness of screening tests, and the policies of each blood transfusion center is essential.

KEYWORDS

blood donors, blood transfusion, hepatitis, infection, prevalence

## 1 | INTRODUCTION

Blood transfusion safety is one of the most critical tasks in blood transfusion centers, and to achieve this, screening for transfusion-transmitted infections (TTIs) is of paramount importance.[1] Occult hepatitis B infection (OBI) is a TTI characterized by an hepatitis B virus (HBV)-DNA load of less than 200 IU/mL in serum of patients with hepatitis B surface antigen (HBsAg)-negative. Despite their tiny amounts of HBV-DNA, some HBsAg-negative blood donors may transmit the virus through blood products (1.49 per million).[2] This

problem is one of the main concerns of blood transfusion centers regarding viral hepatitis after blood transfusion.

Although the prevalence of HBV in blood donors has been significantly reduced with the advent of HBsAg screening, this method is not effective for OBI screening due to the lack or undetectability of HBsAg.[3] One way to screen for OBI is to use an anti-HBc test. Despite its cost-effectiveness, this method can defer healthy donors from blood donation (8.9%, 384 of 4313).[4] This type of exemption is due to the false positives of the anti-HBc test. Another method that is also used for OBI screening is NAT (nucleic acid test). This method does not have the disadvantages of the anti-HBc method, yet it is considered an expensive method.[5] Given the above, OBI screening in blood transfusion centers has become one of the most challenging tasks for which blood transfusion centers have adopted different strategies and sought various solutions. This review study aimed to appraise the challenges of OBI screening and its associated do's and don'ts in blood transfusion centers.

## 2 | METHODS

### 2.1 | Search strategy

In this review study, a search was conducted on the electronic databases of PubMed, Web of Science, Scopus, Ovid, Irandoc, and Magiran from January 2005 to December 2020. The main inclusion criteria were as follows: Cross-sectional studies containing data on OBI prevalence among blood donors without age and sex restrictions were included in the study. Secondary inclusion criteria included studies on HBV prevalence among blood donors. Studies with incomplete data on the prevalence of OBI were excluded (Figure 1).

## 3 | OCCULT HEPATITIS B INFECTION

### 3.1 | Definition

OBI is an undetectable serum HBsAg, and HBV-DNA in serum or liver of patients is less than 200 IU/mL. In this definition, the window period of acute HBV infection is not included.[6] This definition is also used to differentiate false occult B hepatitis, a condition of HBV infection in which HBsAg is not detectable in serum, but HBV-DNA levels are above 200 IU/mL. Serologically, occult hepatitis B is classified as either seropositive or seronegative. In serum-positive occult hepatitis B, serological markers, anti-HBs, and/or anti-HBc can be detected in the serum. In two-thirds of cases, occult hepatitis B is present as seropositive.[7,8]

Case that is similar to seropositive OBI due to the presence of only anti-HBc in the serum is: passive intake of anti-HBc, such as transfusion of plasma-blood products. These should be considered when using only serology-based tests for OBI screening.[9] As a result, these cases may be regarded as false OBI and may defer the donor from donating blood.

### 3.2 | OBI from a molecular point of view

HBsAg glycoprotein is part of the HBV envelope proteins that can be detected by the enzyme-linked immunosorbent assay (ELISA). Major Hydrophilic Region (MHR) is an essential part of this glycoprotein. The predominant epitope in this region is the target of neutralizing antibodies, and it is located between the 124th and 147th amino acids. This area is especially important in detecting the virus by diagnostic kits and the immune system's response to the virus. Thus, mutations in this region alter amino acids and lead to false-negative results obtained using diagnostic tests.[10] The G145R mutation is one of the most common mutations in this region, which reduces the affinity of diagnostic antibodies to HBsAg. False-negative results by ELISA diagnostic kits are the result of this mutation. In other words, HBsAg is present but not detectable with some existing diagnostic kits. Other mutations that have affected MHR include G119R, C124Y, Q129R, S136P, and C139R. One of the reasons for mutations is the inability of the reverse transcriptase enzyme to correct mutations. The reverse transcriptase enzyme (RT) is a protein that is transcripted from the polymerase gene (P gene), and it lacks proofreading activity. Also, because of the overlap between the S and P genes, mutations in the polymerase gene may

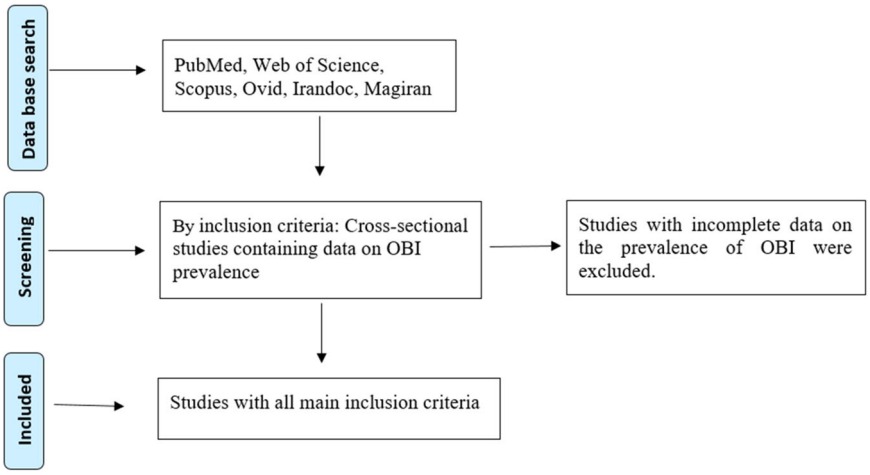


**FIGURE 1** Flowchart of search strategy steps. After searching PubMed, Web of Science, Scopus, Ovid, Irandoc, and Magiran databases, studies were screened by one reviewer. Then, the steps of selecting studies based on the main criteria were done by two reviewers.

**TABLE 1** Prevalence of HBV among Iranian blood donors.

| Year<br>Country | 1998 | 2008 | 2010 | 2016 | 2018 | Reference |
|---|---|---|---|---|---|---|
| Iran | 1.79% | 0.41% | 0.2% | 0.1% | 0.06 | 25–28 |

Abbreviation: HBV, hepatitis B virus.

also alter the S gene, resulting in the failure of HBsAg to be detected by diagnostic kits.[11]

Furthermore, these mutations are also associated with HBV variants. In terms of quantitative and qualitative changes in HBsAg, these variants are enumerated here. First, there is the S-escape-variant that causes a qualitative change in the S protein and is not detected by screening kits. In this variant, the level of HBV-DNA is similar to that in other HBV infections. The next variant is S-promoter-variant that reduces HBsAg secretion. In this case, the level of HBV-DNA does not decrease. Finally, there is the spliced variant, in which the level of HBsAg is low, but HBV-DNA is lower than the level detected by diagnostic methods. This variant is associated with OBI.[12,13] Other factors that reduce HBV-DNA include HBV-hepatocyte genome integration, the inhibitory effect of the immune system by T lymphocytes, concomitant HCV infection, and epigenetic changes.[14,15]

### 3.3 | OBI and clinical implications

OBI is associated with mild to severe clinical symptoms. The severity of clinical symptoms depends on the condition of the host immune system and the amount of virus load. Mild cases include asymptomatic infections such as those found in inactive carriers.[16]

Risk Factors that predispose patients with occult hepatitis B to cirrhosis or liver cancer include the following: elderly patients, diabetic patients, co-infection with HIV, immune deficiency, inflammation, concomitant infection with HCV, and transplantation.[17,18]

### 3.4 | Risk of transmission and infection of occult hepatitis B in patients

The risk of transmission and infection of occult hepatitis B in blood recipients are directly related to the number of blood products transfused and the type of blood product (the risk of transmission in plasma products being higher).[19,20] The immune system of blood recipients has an influential role in the infectivity of OBI. In immunosuppressed patients, the severity of infection is higher (the mortality rate: 21%–67%).[21]

Hemodialysis patients are at a greater risk of OBI (4.2%: 7 of 165) due to factors such as sharing an infected device, suppressing the immune system, and not responding to the HBV vaccine.[22] Thalassemia patients are also more exposed to infectious agents due to continuous packed red blood cell transfusion, so the prevalence of occult hepatitis B in these blood recipients may also increase (32.5%: 26 of 80).[23,24] Therefore, the risk of HBV infection in these patients through OBI donors is probably more important.

## 4 | CHALLENGES OF OCCULT HEPATITIS B PREVALENCE IN BLOOD DONORS

### 4.1 | Prevalence of HBV in Iranian blood donors

The prevalence of OBI is usually high in areas where HBV is endemic. HBV prevalence in Iranian blood donors has decreased from 1.79% in 1998 to 0.06% in 2018 (Table 1).

Many factors play a role in reducing the prevalence of HBV among blood donors. These include improvement in blood donor selection, postdonation counseling, and blood product screening for TTIs.[29,30] Another critical factor are the increased sensitivity of screening kits, confidential unit exclusion, tracking the infectious agent from the recipient to the donor (Trace-back), tracking the infectious agent from the donor to the recipient (Look-back), educating blood donors and encouraging them to donate blood, and improving public health and vaccination programs.[31,32]

### 4.2 | Prevalence of occult hepatitis B in Iranian blood donors

The prevalence of OBI varies among Iranian blood donors. The rates reported by blood transfusion centers of Mashhad, Ahvaz, and Tehran were 0%–4%, and those reported by blood transfusion centers of Isfahan, Shiraz, and Kerman were 0.9%, 0.8%, and 2.36%, respectively. Also, the highest prevalence of OBI (40 of 1000) was reported by Vaez Jalali et al.[33] (In studies Jafarzadeh et al.,[34] Vaez Jalali et al.,[33] Arab Abadai et al.,[35] and Delavaray et al.,[36] it was approximately 14.8 of 1000, 15.4 of 1000, and 23.6 of 1000, respectively). It seems that the difference in the prevalence of OBI is influenced by the sample size and the type of screening methods (Table 2).

### 4.3 | Screening methods and challenges

The screening methods used by researchers to investigate the prevalence of occult hepatitis B are divided into three strategies. The first strategy is to perform the anti-HBc (immunoglobulin M, immunoglobulin G) test on HBsAg negative samples and then on the anti-HBc positive samples. Anti-HBs negative and anti-HBc positive samples are considered OBI positive. In the second strategy, NAT is performed on anti-HBc positive and anti-HBs positive/negative samples. If NAT is positive, these samples are also considered as OBI positive. According to the third strategy, first, NAT is performed on all HBsAg negative samples, and if NAT is positive (HBV-DNA lower than 200 IU/mL), the samples are

**TABLE 2** Prevalence of occult hepatitis B among Iranian blood transfusion donors.

| Author (reference) | Year | City | Screening method | Confirmation of anti-HBc test | Screening Kit | Anti-HBc positive only (%) | Anti-HBc positive/Anti-HBs positive (%) | OBI prevalence (%) | HBV-DNA identification method | Confirmation method for HBV-DNA identification | Sample size |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pourazar et al.[37] | 2005 | Isfahan | ELISA | No | RADIM | 8 | – | 0.9 | PCR | – | 545 |
| Behbahani et al.[38] | 2006 | Shiraz | ELISA | No | – | 6.55 | – | 0.8 | – | – | 2000 |
| Amini Kafiabad et al.[39] | 2007 | Tehran | ELISA | Repetition | ETI-AB-COREK-2 | 11.5 | 78 | 0.05 | PCR | Repeat the test and recall the donor | 2000 |
| Jafarzadeh et al.[34] | 2008 | Rafsanjan | ELISA | No | RADIM | 5.18 | 42.8 | 1.48 | PCR | – | 270 |
| Arab Abadai et al.[35] | 2010 | Rafsanjan | ELISA | No | RADIM | 9.5 | – | 1.54 | PCR | – | 3700 |
| Ramezani et al.[40] | 2010 | Tehran | ELISA | No | DIA.PRO | 2.07 | – | 0 | Real-time PCR kit (artus HBV LC PCR Kit) | – | 531 |
| Khamesipour et al.[41] | 2011 | Rasht | ELISA | No | DiaSorin | 3.8 | – | 0.05 | Real-time PCR kit (artus HBV LC PCR Kit) | Repeat the test with a Homemade PCR kit | 2041 |
| Delavaray et al.[36] | 2011 | Kerman | ELISA | Repetition | Enzygnost Anti-HBc Siemens | 8 | – | 2.36 | PCR Roboscreen HBV detection kit | – | 1525 |
| Vaez Jalali et al.[33] | 2013 | Tehran | ELISA | No | ELISA anti-HBc, Biokit | 8 | – | 4 | Nested-PCR | – | 1000 |
| Alizadeh et al.[42] | 2014 | Tehran | ELISA | No | DADE Behring | 9.98 | 78.4 | 0 | Real-time PCR kit (artus HBV LC PCR Kit) | – | 5000 |
| Abbasi et al.[43] | 2016 | Ahvaz | ELISA | No | DIA.PRO | 4.3 | – | 0 | Nested-PCR | – | 184 |
| Karimi et al.[44] | 2016 | Kermanshah, Ahvaz | ELISA | Repetition | DIA.PRO | 4.9 | 27.7 | 0 | PCR (POOL method) | Repeat experiments with Real time-PCR | 86,182 |
| Tabar et al.[45] | 2019 | Golestan | ELISA | Repetition | DIAPRO, | 11 | 78 | 0 | Real-time PCR kit (artus HBV LC PCR Kit). | – | 3500 |
| Bahrami et al.[4] | 2020 | Golestan | ELISA | Repetition | Diapro, Siemens | 2.6 | – | 0 | Nested-PCR (POOL method) | Repeat experiments with Real time-PCR | 4313 |

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HBV, hepatitis B virus; OBI, occult hepatitis B infection.

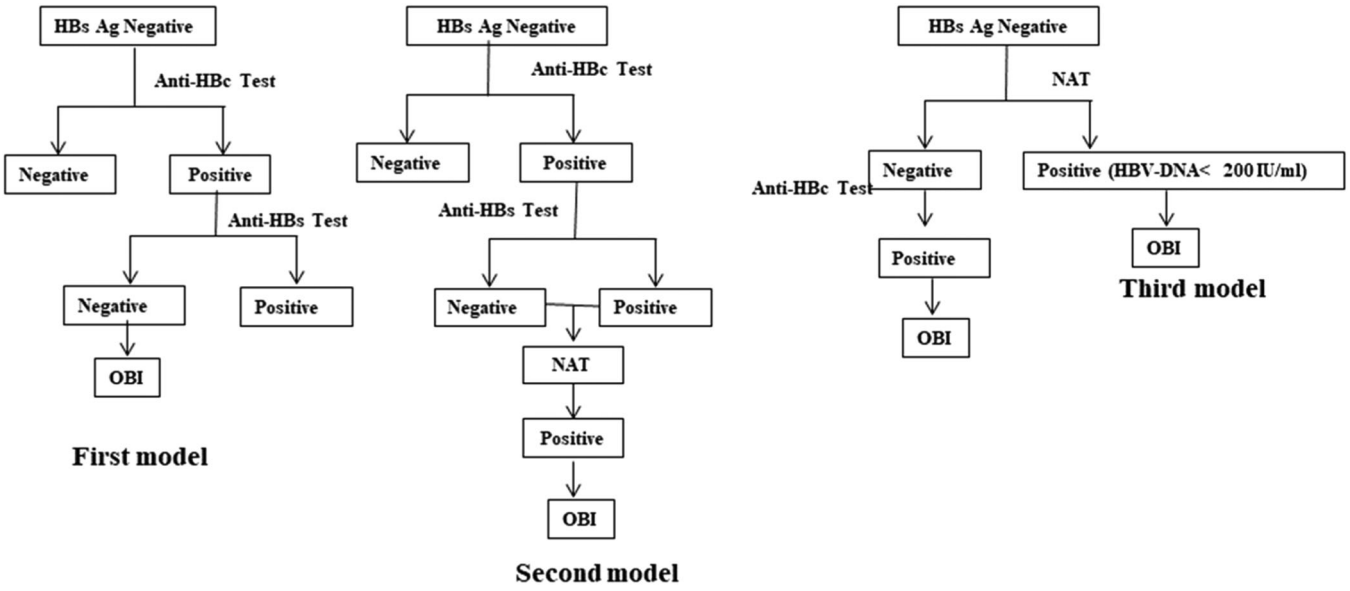


**FIGURE 2** Different OBI screening strategies: in the first strategy, screening is performed only by the anti-HBc test, while in the second strategy, a complementary NAT test is used. In the third strategy, either NAT test or anti-HBc is used. OBI, occult hepatitis B infection.

considered OBI positive. In case NAT is negative, an anti-HBc test is performed on these samples. If the result is positive, these samples are also considered OBI positive (Figure 2).[46,47]

Furthermore, the variable prevalence of OBI, despite reducing the prevalence of HBV from 1998 to 2019 (Table 1), is challenging in Iranian blood transfusion centers. The following factors have been reported to contribute to the changes in the prevalence of OBI.

### 4.3.1 | OBI screening method

The methods used in Iran include anti-HBc/NAT or anti-HBc (Table 2). Despite its high sensitivity (an analytical sensitivity ranging between 3 and 50 IU/mL) compared to serological methods, NAT has a number of limitations. For example, using NAT alone may not detect some cases of OBI. since it has been found that in some cases of OBI, the serum nucleic acid test is negative while it was positive for anti-HBc. In this case, HBV-DNA was detected in the liver biopsy specimen.[48,49] The use of anti-HBc testing for OBI screening also has been a matter of debate among blood transfusion centers. Given that the test results may include false-positives (8%–10% of blood donors).[50,51] Performing this test alone in areas with a high prevalence of anti-HBc may bring about deferral of more blood donors and reduce blood reserves.[52,53] On the other hand, due to the cost-effectiveness of this test, some blood transfusion centers use it as a screening method. As a result, the use of NAT/anti-HBc test or a combination of both tests depends on highly endemic HBV areas with high anti-HBc prevalence and the cost-effectiveness of these laboratory tests. The combined method is usually more effective than anti-HBc or NAT testing alone.

### 4.3.2 | Sensitivity of screening kits

Since occult hepatitis B screening is based on selecting HBsAg negative samples, it is important to use HBsAg detection kits with appropriate sensitivity. For example, in Wantai and Murex kits, this sensitivity is 2 and 0.03 IU/mL, respectively. In developed countries, ELISA and chemiluminescence methods with a sensitivity of less than 0.08 IU/mL are used to detect HBsAg, which can also detect HBsAg muted.[54,55] The use of more sensitive kits leads to the detection of more cases of HBsAg in blood donors (ETI-MAK-4 (DiaSorin), analytical sensitivity: 0.05 IU/mL: 10,866 HBV infection of 1,494,282 blood donors and Enzygnost HBsAg 5.0 (Dade Behring), analytical sensitivity: 0.2 IU/mL: 973 HBV infection of 1,603,149 blood donors).[25] As a result, it is essential to have more sensitive kits that can detect the entire MHR. Therefore, the use of less sensitive HBsAg detection kits may have overestimated OBI.

### 4.3.3 | False OBI

False-positive OBI has also been influential in overestimating the prevalence of OBI. In fact, most OBI reports are false (18.3%, 40 of 219 HBsAg-negative subjects).[56] Confirmation of initially positive OBI cases plays an important role in reducing false-positive reports (initially positive OBI: 21, confirmed OBI: 3 of 21). The steps of confirming the positive results are as follows: donor recall and resampling, performing high-sensitivity NAT, determining viral load, phylogenetic analysis of virus genome, and monitoring via Trace-back and Look-back. These virus samples can be considered positive when the virus load is less than 200 IU/mL and the virus genome analysis shows MHR mutations.[41,57]

## 5 | RISK OF OCCULT HEPATITIS B TRANSMISSION THROUGH BLOOD TRANSFUSIONS: DO'S AND DON'TS

The use of OBI-positive blood products plays an important role in infecting blood recipients. The following are effective in transmitting OBI from blood donors to blood recipients: The rate of virus load (in a high load of the virus, the possible transmission of the virus is higher) and, the type of the units of transfused blood product (the risk of transmission of the virus through plasma products such as FFP is 85% as opposed to that through platelet products [51%] or packed red blood cells [24%]). The number of blood products also plays a role in the risk of transmission of the virus. The injection of two units of FFP will have a higher risk of transmission of the virus than one unit of FFP.[58,59] Immune system defects of blood recipients also lead to an increase in the severity of infection. For example, OBI in a patient with a defective immune system is associated with more severe clinical complications.[60] As a result, there is still a risk of OBI transmission from blood products to blood recipients (especially in cases such as hemodialysis patients or cancer). In other words, OBI screening is mandatory in this situation.

On the other hand, the disadvantages of OBI screening include the following: Exemption of blood donors due to a positive anti-HBc test (in areas where HBV is endemic, anti-HBc screening can lead to the exemption of blood donors), and the high cost of the NAT screening kit (in developing countries where HBV is endemic, OBI screening by a NAT kit will lead to high financial costs for the blood transfusion center). In these cases, OBI screening is a challenging.

Depending on what was discussed above, blood transfusion centers can adopt different strategies depending on the risk of OBI transmission. Recommend that, blood transfusion center to review OBI risk assessment and determine OBI transmission risk reduction strategies, accordingly. These strategies include OBI screening, pathogen inactivation of blood products for high-risk patients, educating and encouraging donors to donate blood, increasing the number of continuous donors, and HBV vaccination of donors.

## 6 | CONCLUSION

Estimating the prevalence of OBI in blood transfusion centers plays an important role in transfusion risk assessment and screening strategies. Determining an appropriate screening strategy based on prevalence status, the cost-effectiveness of screening tests, and the policies of each blood transfusion center is essential. Although the risk of OBI transmission in Iranian blood donors is probably low, it is still a challenge for high-risk patients.

### AUTHOR CONTRIBUTIONS

**Mohammad Hossein Ahmadi**: Writing—review & editing. **Zohreh Sharifi**: Writing—review & editing. **Ali Ghasemi**: Writing—review & editing. **Sadegh Abbasian**: Conceptualization; Methodology; Project administration; Supervision; Validation; Writing—original draft; Writing—review & editing.

### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### TRANSPARENCY STATEMENT

The lead author Sadegh Abbasian affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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