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Occult Hepatitis B Infection and Its Role in Blood Safety: a Review

Alborzi AM [1], Kiani Ghalesardi O [2], Bamdad T [1], Pourfathollah AA [3], Jalalifar MA [2], Shahjahani M [4], Kazemi Arababadi M [5], Dehghani Fard A[4], Saki N [2]*

1- Department of virology, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran.

2- Research Center of Thalassemia and Hemoglobinopathy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

3- Department of immunology, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran.

4- Department of hematology, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran.

5- Department of Microbiology, Hematology and Immunology, Faculty of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

***Corresponding Author:** Saki N, Email: najmaldinsaki@gmail.com*

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Abstract

Background: Blood transfusion plays a great role in public health and the blood safety still has remained a main concern. HBV has been considered as one of the most prevalent blood borne infections. It is estimated that chronic HBV affects 350-400 million people worldwide. Comprehensive knowledge about HBV has high importance in Iran due to high number of blood dependent patients.

Material and methods: The data used in this research are derived from articles obtained by searching keywords like occult hepatitis B infection, thalassemia, hemophilia, hemodialysis, co-infection and blood transfusion in databases including PubMed, Google Scholar and Scopus. The prevalence, genotypes, HBV-HCV co-infection, HIV-HBV co-infection and their role in blood transfusion and blood safety are discussed in this review article.

Results: Iran is in intermediate endemicity region and studies have reported that between 10–60% of the Iranian population has the evidence of HBV infection, with 2-7% being chronic carriers. In blood donors the rate of infection is lower than general population. The occult hepatitis B infection is the main concern in blood safety due to transmission of the HBV via seronegative blood components. Iranian researches have reported a 1-2% prevalence of occult hepatitis B infection among Iranian blood donors.

Conclusion: Based on our review findings the prevalence of HBV and occult hepatitis B infection in Iran is moderate, which shows the importance of taking necessary steps to reduce the transfer of infection via blood and its components.

Keywords: Hepatitis B virus, prevalence, blood donor, safety.

Introduction

Hepatitis B virus is a noncytopathic DNA virus causing acute and chronic infection in patients. This virus is the tenth cause of mortality around the world. Currently, over 400 million individuals (5% of world population) are infected with the virus [1]. Although, blood transfusion has been considered as a lifesaving treatment in many cases such as patients with anemia, trauma and obstetric problems, it can also be dangerous because of post transfusion infections including viral and bacterial pathogens [2]. HBV has been considered as one of the most prevalent blood borne infection agents [3]. Precise control of donor selection process and checking all donors for blood transfusion transmissible pathogens can reduce the risk of infectious agents, but the window period is still inevitable [4, 5]. Hence, blood transfusion should be recommended only if there is no replacing remedy. The risk of hepatitis B transmission through blood transfusion has obviously been reduced via HBsAg screening in recent years [6]. The screening of drawn blood for HBsAg began in 1970s, so the incidence of hepatitis B through blood transfusion was greatly reduced. However, many reports published around the world still emphasize on the transmission of this virus through blood transfusion [7, 8].

Although, HBsAg screening using ELISA (Enzyme-Linked Immunosorbent Assay) technique

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is used to reduce transmission of HBV through blood and blood products, many reports indicate HBV transmission through HBsAg negative bloods[7, 9] showing that the study of blood products only by means of detecting HBsAg is not enough to recognize sample HBV infectivity [9, 10] since HBV infection may exist without detectable HBsAg, as occult hepatitis B infection (OBI) [11].

OBI is characterized by a low level of virus replication and absence of HBsAg in screening tests [12] . OBI is defined by detection of HBV DNA in serum and/or liver of patients and the absence of HBsAg, with presence or absence of anti-HBc or anti-HBs [9, 11-18]. Despite the worldwide HBV vaccination program, hepatitis B is still problematic in blood products [19]. Based on the fact that, OBI can be considered as an important risk factor for HBV transmission in the blood recipients, many researchers have studied the prevalence of OBI in blood donors, and the risk of OBI transmission by means of blood and blood products. The main aim of this review article was to collect recent data regarding OBI prevalence among blood donors with emphasizes on Iranian blood donors.

HBV Prevalence

It is estimated that chronic HBV affects 350-400 million people worldwide, with a mortality rate of 500,000 to 1.2 million deaths per year caused by acute or chronic hepatitis B infection, cirrhosis and hepatocellular carcinoma (HCC) [20]. For the year 2000, the model estimated that 620,000 patients died worldwide from HBV-related causes: 580,000 (94%) from chronic infection-related cirrhosis and HCC and 40,000 (6%) from acute hepatitis B [21]. The model of surviving birth cohort, for the year 2000, estimated that without vaccination, 64.8 million would become HBV-infected and 1.4 million would die from HBV-related disease [21, 22]. Infections acquired during the prenatal period, in early childhood (<5 years old), and in 5 years old children account for 21%, 48%, and 31% of deaths, respectively [21]. Furthermore, 4.5 million new HBV infections occur worldwide each year, of which a quarter progress to liver disease [23]. HBeAg-negative chronic hepatitis B and OBI are two special clinical entities, of which the prevalence and clinical implications remain to be explored [9].

Interestingly, the predominant transmission routes of diseases are different according to the endemicity of HBV infection [24]. In areas of high HBV endemicity, prenatal transmission is the main route of transmission, whereas in areas with low HBV endemicity, sexual contact amongst high-risk adults is the predominant route [25]. The prevalence of HBV infection varies markedly throughout the world [26]. In a study by Arababadi et al. to identify the status of OBI among blood donors in Rafsanjan-Iran, it

Table1: HBV prevalence in different groups of Iranian population.

Type of sample	HBsAg/HBcAb/ HBsAb	Location	sample number	Duration	Reference
Healthy Iranian	62 (1.5%) seropositive: $HBsAb^+$ 15%, $HBcAb^+$ 6.3 %, 12.5% were positive for both.	Hormozgan	4087	2008-2009	(51)
Blood donors	352 (9.5%) $HBcAb^+$	Rafsanjan	3700	2009	(52)
kidney transplant recipients and donors	HBV S $gene^+$ in 102	Fars	273	2005-2008	(53)
Male injection drug abusers	$HBsAg^+$ (5.8%)	Tehran	499	2006	(54)
Injection drug abusers	$HBsAg^+$ (4.7%)	Hormozgan	249	2002	(55)
Homeless men	87 HBV positive: 8$HBsAg^+$ and 86 HBc Ab^+	Tehran	202	2007	(56)
Hemodialysis patients	$HBsAg^+$ (5.1%)	Khuzestan	214	2005-2006	(57)
Beta-thalassemia patients	$HBsAg^+$ (1.5%)	Multicenter	732	2006	(58)

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was observed that 16.1% of HBsAg negative and anti-hepatitis B core (anti-HBc) positive (HBsAg-/anti-HBC+) blood donors (57/352) were HBV DNA positive, which is 1.54% (57/3700) of the total collected samples. In other words, 1.54% of blood donors were infected by OBI [27]. Also, in another study done by Arababadi et al. which also evaluated two different populations regarding the prevalence of OBI among blood donors, they have reported that of 545 (0.92%) donors from Isfahan and 270 (1.45%) from Rafsanjan were infected by OBI, respectively [28]. In a study by Behbahani et al., from 2000 blood donors referred to a blood transfusion center in Fars province, Iran, 0.8% were infected by the clinical form of OBI [29]. Amini et al. also evaluated 2000 donors from Tehran, and found that 0.15% of blood donors carried OBI [30]. Collectively, studies on Iranian population have indicated 1-2% prevalence of OBI among Iranian blood donors [27].

García-Montalvo et al. from Mexico showed the prevalence of OBI to be 0.7% among blood donors[31]. OBI has also been detected in patients without hepatic disease including blood donors with normal hepatic enzymes and in general population [16]. OBI has been reported in 0.1- 2.4% of HBsAg negative and anti-HBc positive donors in Western countries like United States [32, 33]. The incidence of OBI in the Asian population with normal liver enzymes has been reported to be 7.5-16% [34-36]. OBI has also been observed in 45-50% of intravenous drug users or hemophilia patients [37], in up to 36% of the hemodialysis patients [38, 39], and in 8-51% of HIV positive patients [40, 41].

High endemicity

Hepatitis B is highly endemic in populated developing regions such as Southeast Asia, China, Sub-Saharan Africa and the Amazon Basin, where at least 8% of the population are chronic carriers of HBV. In these areas,70–95% of the population show past or present serological evidence of HBV infection. Most infections occur during infancy or childhood. Since most infections in children are asymptomatic, there is little evidence of acute disease related to HBV, but the rates of chronic liver disease and liver cancer in adults are high [42].

Table2: Common HBV genotypes in Asia, Middle East and Iran.

Country	Genotype	Sample	Location	Year	Reference
Iran	D	Asymptomatic HBV infected patients	Rafsanjan	2009	(66)
		Patients with HBV-associated HCC	Iran	2000-2007	(67)
		HBV-infected patients	Iran	2004-2007	(68)
		HBV-infected patients	Southwest Iran	2007	(69)
		HBV-infected patients	Tehran	2002 - 2006	(70)
		HBV-infected patients	Tehran	2004	(71)
		HBV infected Blood donors	Southwest Iran	2008	(29) (72)
Pakistan	D (70%) and (A 20%) and AD (10%)	HBsAg positive patient	Karachi	2006 - 2007	(73)
Philippine	A (28%) and C (26%)	Chronic HBV-infected patients	Cebu	2008	(74)
Egypt	C	HBV infected patients	Ismailia	2000-2003	(75)
Korea	C	HBV-infected patients	Several cities and harbors throughout the Korean peninsula	2008	(76)
Hong Kong	B (49%) and C (51%)	Chronic hepatitis B patients	Hong Kong	2008	(77)

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Intermediate Endemicity

Hepatitis B is moderately endemic in parts of eastern and Southern Europe, the Middle east, Japan, and parts of South America, between 10–60% of the population have evidences of infection and 2-7% are chronic carriers [9]. There is also intermediate prevalence of HBV with a 2.14% infection rate in Iran [43]. HBV related disease is common in these areas because of infection in adolescents and adults; however, the high rates of chronic infection are mostly due to infections occurring in infants and children [43, 44] (Table 1).

Low Endemicity

The endemicity of HBV is low in most developed areas like in North America, Northern and Western Europe and Australia. In these regions, HBV infects 5-7% of the population, and only 0.5-2% of the population are chronic carriers [9].

Incidence and risk of OBI in recipients of blood products

The risk of OBI through transfusion is significantly higher than HIV-1 or HCV [45]. HBV transmission from OBI positive donors with a low level of HBV DNA has been reported [19]. HBV transmission is also dependent upon viral load in blood components [45]. In a study, it was demonstrated that four out of five OBI donors who carried the D genotype and another one with A2 genotype were capable of transmitting hepatitis to blood recipients [19]. Therefore, it seems that HBV genotype can be considered as important risk factor in HBV transmission via OBI infected patients.

OBI incidence in hemophiliacs

Hemophiliacs who receive high quantities of blood and its components are at high risks of infection by blood transfusion [46]. Previous reports from Pakistan [47] and Japan [48] have demonstrated that the prevalence of OBI among hemophiliacs is 1.73% and 2.51%, respectively.

Incidence of OBI in thalassemia patients

Thalassemia patients, like hemophiliacs who receive great quantities of blood and blood components, are at risks of OBI transmission [49]. In a report from India, it was reported that OBI prevalence was 31.4% among thalassemia patients[50], while our previous study on 60 thalassemic patients identified that none of patients were infected by OBI [49].

Table3: HBV-HCV co-infection prevalence from different studies in Iran.

Target population	Location	Number of patients under study	Comments	Year	Reference
First time blood donors	Bushehr	51884	HBV-HCV co-infection 0.013 %(7 persons).	2010	105
Chronic hepatitis C virus	Tehran	103	20 Patients affected with OBV.	2009	106
Pregnant women	Malekan	680	3(0.49%) pregnant women were HBV/ HCV co-infection.	2007	107
HBsAg-positive subjects	Golestan	138	Anti-HCV antibody was positive in 17(12.3%) of the 138 subjects.	2006	108
Chronic liver disease (CLD) patients	Tehran	35	77.1 percent of 35 patients were HCV positive and 8(22%) of these were occult HBV infection.	2005	109
Chronic HBV patients	Tehran	264	12 patients (4.54%) were positive for anti-HCV antibody.	2011	110
Injection drug users (IDUs)	Tehran	899	HBV/HCV co-infections were 21.0%.	2010	111
HIV positive patients	Tehran	201	HBV and HCV coinfection was observed in 73 of 201(36.3%) respectively.	2009	112

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Genotype

There are 8 HBV genotypes (A-H), which were identified based on an intergroup divergence of 8% or 4% in the S nucleotide sequence of the gene[10]. HBV genotypes are known to be geographically segregated [59]. Genotype A is pandemic and most prevalent in northern Europe, North America, and central Africa. Genotypes B and C have been observed in Southeast Asia and the Far East. Genotype D is distributed worldwide and is most prevalent in the Mediterranean region. Genotypes E and F are prevalent in West Africa and in Amerindian population, respectively [60]. A few cases of HBV/E in the Americas suggest a relatively recent HBV/E expansion in the population in America, because of the high HBV/E prevalence in Africa coupled with the high volume of the African American slave trade that took place between the 17th and the 19th century [30, 61-63]. Recently, genotype G was identified in the USA and France [64]. Genotype H is found in Central America [65]. Table 2 illustrates common HBV genotypes in Asia, Middle East and Iran.

Complications

Hepatocellular carcinoma

As early as 1970, chronic infection with the HBV was noted to be associated with the development of HCC [78]. It has been estimated that 80% of HCC worldwide is etiologically associated with HBV [79], and hepatitis C virus is the second etiology of HCC[16]. It is estimated that 550,000-600,000 of new HCC incidence happened in year 2010 [80]. HBV belongs to a group of oncogenic viruses known as hepadnavirus and can integrate its DNA into the genome of the infected hepatocytes. It has been established that HBV DNA integration to the hepatocytes genome can lead to HCC. Interestingly, the integration has been observed in about 80% of human HBV infected patients [81]. The hepatitis B x gene (HBx) product has been implicated in HCC, because it is a transcriptional activator of various cellular genes associated with growth control[82]. A recent longitudinal study of 3,653 HBsAg-positive subjects in Taiwan revealed that elevated serum levels of HBV DNA (>10,000 copies/mL; ~ 2000 IU/mL) at baseline was a strong predictor of subsequent development of HCC, independent of serum hepatitis B e antigen (HBeAg) status, serum aminotransferases levels or the presence of cirrhosis [83]. Genotype B is more inclined to HCC development, whereas, genotypes A and C cause hepatitis and cirrhosis more than HCC [84]. In patients with HCC, 14-100% are positive for anti-HBc and 8–87% of patients are not positive for any markers which are considered to be OBI [16].

Table4: HBV- HIV co-infection in different populations, Iran.

Target population	Location	Number of patients under study	Comments	Year	Reference
hronic HBV patients	Tehran	264	1 patient (0.37%) was positive for anti-HIV antibody	2011	110
IV Drug abusers (IDU) patients	Tehran	899	HIV/HBV, co-infections were seen in 7.8% of patients	2010	111
HIV positive patients	Tehran	201	The maximum prevalence of HBV-HIV co-infection was seen in intravenous drug abusers; 61.2%	2009	112
HIV infected Patients	Isfahan	130	15 subjects (11.5%) were HBsAg positive, 100 (77%) were anti-HCV positive and 12 subjects (9.2%) were positive for both.	2010	115
IV Drug abusers (IDU) patients	Ahwaz	154	104 patients (67.53%) were HIV positive. Among HIV infected, HBsAg were positive in 44.23% of patients.	2007	116

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Hepatitis-associated Aplastic anemia (HAAA)

HAAA is an uncommon but distinct variant of Aplastic anemia in which pancytopenia appears two to three months after an acute attack of hepatitis. HAAA occurs most frequently in young males and is lethal if left untreated. The etiology of this syndrome is proposed to be attributed to various hepatitis viruses such as hepatitis A [85], B [86, 87], C [88] and G [89]. It has also been documented that HAAA is not related to age, sex and the severity of hepatitis [90]. It has been predominantly found in children [91], adolescent boys and young men [92, 93].

Co-infection with other transfusion transmitted infections

HCV-HBV co-infection

HBV and HCV infections can occur simultaneously. These viruses are responsible for multiple liver damages ranging from minor histological disorders to liver cirrhosis and HCC 9[4, 95]. HBV and HCV co-infections can lead to more aggravated pathologic changes of liver and lower response rates to anti-HCV therapy [96].

HBV and HCV co-infection is frequently found in intravenous (IV) drug abusers (IDU, 42.5%)[94], patients on hemodialysis (3.7%)[95], patients undergoing organ transplantation (8%) [97], and beta-thalassemic patients (10%)[98], which means they are the high risk population for concurrent HBV and HCV infections. Combined HBV/HCV infection also is possible because of common mode of viral transmission [99]. It is particularly frequent in areas where the two viruses are endemic, and in subjects with high risk of infection through parenteral routes. Depending on the geographic region, less than 1% to 48% of patients with HCV infection have been reported to be also positive for hepatitis B surface antigen (HBsAg) [100, 101], while, 3 to 30% of those with HBV infection are anti-HCV positive [102, 103]. In a study, the prevalence of occult HBV in HCV patients was from 0 to 52.3% [104]. The

Table5: HBV prevalence among different regions among blood donors (Iran).

HBsAg/ HBcAb	Location	Sample number	Year	Reference
11 (2.1%) HBcAb	Arak	531	2008	(144)
(2.07%) HBcAb	Iran/Tehran	531	2008	(145)
(1.08 %) HBsAg	Ghazvin	39598	2000-2002	(146)
(8%) HBcAb	Isfahan	545	2005	(147)
0.4% HBsAg	Jahrom	3000	2001-2003	(148)
(9.51%) HBcAb	Rafsanjan	3700	2008	(149)
(0.68%) HBsAg	Arak	11615	2004	(150)
(0.8%) HBsAg	Hamadan	18306	2004-2005	(151)
0.23% HBsAg	Boushehr	20294	2006	(152)
(0.57%, 0.52%, 0.53%, 0.53%) HBsAg	Shiraz	507531	2000-2005	(153)
0.45% HBsAg	Gilan	221508	1997–2002	(154)
1.79% in 1998 to 0.41% in 2007	Iranian Blood Transfusion Organization (IBTO)	14599783	1998-2007	(155)
0.56% for HBV	Tehran	6,499,851	2004-2007	(156)
1.78% HBsAg	Shahrekord	11,200	2009	(157)
HBcAb (4.7%) and HBsAb (5.3%)	Khorramabad and Borujerd	1000	2008	(158)
0.47% HBsAg	Hamadan	8468	2008	(159)
0.6 % HbsAg	Ahwaz	25772	2005	(160)
0.8 % HbsAg	Ahwaz	39032	2007	(161)

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results of some recent studies about HBV/HCV co-infection in Iran are presented in table3.

HIV-HBV co- infection

HBV and HIV share common, mainly sexual, routes of transmission. Therefore, the prevalence of serological markers of HBV is higher among HIV infected patients than in non-HIV infected individuals [104, 113]. It is estimated that 10% of HIV infected patients in the United States and Europe are chronically co-infected with hepatitis B virus (HBV). HIV-HBV co-infected patients have higher rates of liver-related morbidity and mortality compared to patients infected with either virus alone [114]. Table 4 summarizes the recent studies about HBV/HIV co-infection in Iran.

Immunological response

HBsAg seroclearance may result in a decreased risk for HCC in the hepatitis B infected patients[40]. It will be worthwhile identifying any immune mechanisms that might contribute to HBsAg seroclearance, as they may provide targets for immunotherapy. The contributing mechanisms include acquired CD4+ and CD8+ T cell responses[117], innate immune responses [118] and mutations in the HBsAg arising from genetic drift [119]. The possibility of HBsAg seroclearance resulting from an acquired immune response to antigens within the envelope proteins is of particular interest [120]. In a study by Liang et al. [120] it was observed that the frequency and magnitude of antigen-specific T cell responses was also higher in the HBsAg seroclearance group than in subjects with immune tolerance. However, the T cell responses in the seroclearance group were almost exclusively against core antigens and only a small number of low level responses to envelope antigens were detected [120]. Recovery from acute hepatitis B is the result of a combination of cellular and humoral immune responses, whereas neutralizing antibodies (Abs) against HBsAg appear after recovery. Cellular immune responses are generally detectable before the synthesis of neutralizing Abs [121] and precede the rise of serum alanine aminotransferase (ALT) levels [122]. The clearance of HBeAg and HBsAg are mediated by cells of the innate immune response, especially NK cells [123, 124] and by CD4+ and CD8+ T cells that clear HBV by cytolytic [125], noncytolytic and cytokine-mediated mechanisms [123, 126].

Interestingly, our previous studies revealed that some features of immune responses of chronic and occult HBV infected patients are disrupted. For instance, we have previously shown that CCR5 (the receptor for CCL5, CCL4 and CCL3) has decreased on the NK cells of occult [127], chronic (unpublished data) and also T cytotoxic lymphocytes of occult[128] and chronic [129] HBV infected patients. We have also shown that serum levels of inflammatory cytokines are decreased, while, anti-inflammatory cytokines increased in the occult and chronic HBV infected patients in comparison to healthy controls [27, 130-132].

Additionally, Vitamin D3 receptor (VDR3) appears to be involved in antiviral immune responses. The polymorphisms in the T/T allele of exon 9 of VDR is possibly associated with OBI, thus it can be concluded that VDR and its functional polymorphisms are likely to be related to sensitivity and resistance of the immune system to HBV in OBI patients [133]. Therefore, it seems that the long term infected patients suffer from impaired immune responses against HBV and future studies can be considered to clear the responsible mechanisms [134].

HBV and blood banking

Blood transfusion is still one of the most important therapeutic approaches all over the world[135]. Therefore, paying attention to complications among recipients such as post transfusion infection is necessary [136]. Indeed, supplying safe blood and blood products is the main purpose of any blood transfusion service [137]. This can be achieved by providing the screening protocols of the safe blood donation. Supplying safe blood has been considered as a great concern in some less-developed and developing countries where donors are paid for whole blood collection. Paid donors are mostly from poor economic and social groups selling blood to earn money. This payment system can increase the transmission risk of blood-borne viruses [2].

As most OBI infections are asymptomatic, we can detect them only through screening of large populations. Current tests for this purpose include: 1) Liver biopsy: although diagnosis of HBV DNA in liver is the best method to detect OBI, it is not always possible to perform, and liver biopsy for routine testing of patients has not been approved by FDA [138]. 2) HBsAg detection method; the detection should be performed based on the current WHO

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International Standard for HBsAg [139]. 3) Anti-HBc detection method; Infected donors may have no detectable HBsAg because of the low sensitivity of the assay. Whereas anti-HBc introduces acute, chronic or resolved HBV infections, if donors have negative serologic HBsAg with positive anti-HBc, they rarely have infectious blood products [140]. In fact, anti-HBc test can detect those donors who have a high anti-HBs titer to mimic non-infection conditions [140]. Anti-HBc-positive donors with at least 100 IU/L anti-HBs can donate blood if they have had negative HBV NAT (Nucleic acid Amplification Testing) results [141]. Diagnosis of HBV DNA in anti-HBc individuals significantly helps to identify OBI patients [138]. However, this method has two drawbacks that cannot be ignored: first it cannot detect the seronegative WP infections, and second it is not practical in regions where anti-HBc incidence is higher than 10% [142]. 4) Viral genome detection method: this method is the gold standard of identifying people with OBI [143]. Currently, real-time and nested polymerase chain reactions (PCR) are used to perform this test [139]. HBV NAT has been used for detecting the presence of HBV nucleic acid with high sensitivity and specificity (see table 5). This PCR-based technique increases the safety of blood and blood products when simultaneously performed with serologic tests mentioned, but is still unable to completely close serologic window period [7]. In some countries, including the USA and Japan, parallel screening for HBsAg and HBc-Ab is performed in all donor samples; in contrast, in India and Iran, HBc-Ab is not in the screening program for blood donors [8]. The molecular diagnostic tests such as NAT are not performed routinely in our country yet.

Conclusion

Based on our review findings, the rate of HBV prevalence and OBI in Iran is moderate. Although the blood transfer safety has improved, the use of HBsAg as the only marker to detect HBV infection in Iran does not perfectly meet blood safety goals. Considering the risk of transmission of OBI through blood products to recipients, and the fact that the available methods to identify people with OBI are not currently used by Iranian Blood Transfusion Organization, to prevent the spread of this infection in our country in addition to HBsAg detection method, Anti-HBc and viral genome detection should be applied for detection and identification of OBI contaminated blood products. This indicates the importance of taking necessary steps to reduce the transfer of infection via blood products.

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