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ORIGINAL ARTICLE

Significance of Anti-HBc Screening in Detecting Occult Hepatitis B Infection in Hemodialysis Patients of Resource-Limited Settings

Azim MAU[1], Kabir ME[2], Haque MO[2], Bashar MA[2], Ansary EAF[3], Alam MR[4]

Abstract:

Introduction: *Patients with chronic kidney disease (CKD) undergoing hemodialysis (HD) are at increased risk of HBV infection. Occult hepatitis B infection (OBI) is defined by the presence of HBV DNA in the blood and/or hepatocytes in the absence of detectable hepatitis B surface antigen (HBsAg), with or without anti-HBc antibodies. Persistent OBI may lead to progressive liver damage, including fibrosis, cirrhosis, and hepatocellular carcinoma. Anti-HBc is considered a potential surrogate marker of OBI. This study aimed to determine the prevalence of anti-HBc positivity as a marker of OBI in hemodialysis patients.*

Methods: *This cross-sectional study included 220 HBsAg-negative patients receiving maintenance hemodialysis in a tertiary care center in Khulna, Bangladesh, for at least for more than 3 months. Anti-HBc antibodies were detected using enzyme-linked immunosorbent assay (ELISA), and qualitative detection of HBV DNA was performed using real-time polymerase chain reaction (PCR). Data were analyzed using SPSS, and a p-value of <0.05 was considered statistically significant. Descriptive and inferential analyses were performed.*

Results: *A total of 220 patients were included, with a mean age of 47.87 ± 13.46 years; 67% were male. Anti-HBc antibodies were detected in 85 (39%) patients, with a mean age of 50.08 ± 12.74 years. Among anti-HBc–positive patients, 60 (71%) were male. The HBV DNA was detected in 2 (0.9%) of the HBsAg-negative patients. Both HBV DNA–positive cases were male and anti-HBc positive. On the other hand, no HBV DNA was detected among anti-HBc–negative patients.*

Conclusion: *The prevalence was low, with only two cases identified. However, a considerable proportion of patients were anti-HBc positive. Anti-HBc may serve as a (pragmatic, low-cost screening tool) important surrogate marker for detecting OBI in hemodialysis patients, particularly in resource-limited settings.*

Keywords: *Chronic kidney disease, Occult hepatitis B infection, Anti-HBc antibody, HBV DNA.*

Introduction

Hepatitis B virus (HBV) is a major public health problem worldwide especially in limited resource countries with minimum facilities for hemodialysis (HD) patients and lack of standard health precautions[1,2]. Despite a decline in the prevalence of HBV infection among hemodialysis populations in Bangladesh[3] and globally[4] over recent decades, largely attributable to universal vaccination programs, the burden of infection remains substantially high[1]. Patients with chronic kidney disease (CKD) undergoing hemodialysis (HD) are at increased risk of blood-borne viral infections, including hepatitis B virus (HBV), due to repeated blood transfusions, frequent invasive procedures, shared dialysis equipment, impaired

1. Muhammed Arshad Ul Azim, Khulna Medical College Hospital, Khulna, Bangladesh
2. Md. Enamul Kabir, Md. Obaidul Haque, Md. Afzalul Bashar, Khulna Specialized Hospital, Khulna, Bangladesh.
3. Eusha Ahmed Fidalillah Ansary, Uttara Adhunik Medical College, Dhaka, Bangladesh
4. Md. Rezaul Alam, Bangladesh Medical University, Dhaka, Bangladesh

Address of Correspondence: Muhammed Arshad-Ul-Azim, Associate Professor, Khulna Medical College Hospital, Khulna, Bangladesh,. Mobile: +8801742141516, E-mail: arshadulazim@gmail.com

host immunity, and a reduced immunological response to HBV vaccination[5,6].

Occult hepatitis B infection (OBI) is characterized by presence of HBV-DNA in the liver or serum (<200 UI/mL) with undetectable hepatitis B surface antigen (HBsAg) with or without HBV antibodies which can be divided into seropositive [hepatitis B core antibody (anti-HBc) and/or hepatitis B surface antibody (anti-HBs) positive] and seronegative (absence of anti- HBc and anti-HBs).[5] OBI patients are at higher risk of progression to liver disease, spreading infection to other patients during dialysis, blood transfusion, and organ transplantation, or early mortality due to acute exacerbation of chronic hepatitis B, fulminant hepatic failure, and development of hepatocellular carcinoma[7]. OBI is one of the most common causes of liver diseases in negative HBsAg patients. Hemodialysis patients have suppressed immunity, which leads to a high prevalence of OBI rather than the general population[8]. The prevalence of OBI in HD patients ranged from 0% to 58% in different studies[5]. Prevalence of OBI is proportionate to the prevalence of HBV infection in that community.

Bangladesh belongs to an intermediate prevalent area of HBV infection (2-7%), which is about 4.2%.[9] Another important issue is that diagnosing liver disease in HD patients based on alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels is difficult due to a weak immune response, which consequently reduces hepatocyte destruction. Detection of HBsAg is a commonly used tool for screening HBV in most developing countries. Though it is effective, the nucleic acid amplification testing (NAT) is expensive for the screening of HBV infection[10]. Occult HBV infection is most commonly seen in patients with anti-HBc as the only HBV serological marker (isolated anti-HBc), and the HBV-DNA detection rate is highest in patients who are anti-HBc positive but anti-HBs negative[7]. The detection of anti-HBc is a very good investigation for tracking OBI, though it accounts for about 80% of OBI patients[7,11]. So, anti-HBc can be considered as a sentinel marker of OBI.[5] The prevalence of anti-HBc in the Bangladeshi general population is 31%[12], and in CKD patients before dialysis is 39.3%[3].

In resource-limited settings, screening based solely on HBsAg is commonly practiced; however, this approach may fail to identify OBI. Although nucleic acid amplification testing (NAT) remains the diagnostic gold standard for detecting OBI, its routine implementation is often constrained by high cost and limited laboratory infrastructure. Anti-HBc has been identified as a practical, low-cost marker that can detect the majority of OBI cases, particularly in patients with isolated anti-HBc positivity. Incorporating anti-HBc testing into routine screening of hemodialysis patients may therefore help identify hidden infections, reduce transmission risk, and improve patient safety where advanced diagnostics are not available.

Therefore, we aimed to determine the prevalence of anti-HBc positivity as a marker of Occult hepatitis B infection (OBI) among hemodialysis patients in Bangladesh to inform policy and practice in resource-limited settings.

Methods

Study design and setting

This prospective cross-sectional study was conducted at the Khulna Specialized Hospital, Khulna, Bangladesh, a 30-bed dialysis unit, providing hemodialysis services in three shifts per day. The study was carried out between January and December 2024.

Study participants

HBsAg-negative patients with end-stage kidney disease who underwent regular maintenance hemodialysis at the hospital constituted the study population. Because the source population was limited and accessible, a census sampling strategy was adopted whereby all eligible patients during the study period were included to maximize statistical precision and minimize selection bias[13]. Participants were recruited using consecutive sampling from patients attending the dialysis unit during the study period. Patients who had been receiving hemodialysis for at least three months were eligible for inclusion.

- All HBs-Ag negative patients.
- Patients who are receiving HD for at least three months for CKD.
- Age ≥18 years who can give consent.

Data collection and blood sample testing

A structured questionnaire was used to collect epidemiological and clinical information, including age, sex, and duration of dialysis. Blood samples were obtained before dialysis, centrifuged immediately, and the separated sera were stored at –20 °C until analysis. All serum samples were screened for total anti-HBc antibodies using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Diapro, Milano, Italy), following the manufacturer's instructions. HBV DNA was extracted from patient samples using a commercial DNA extraction kit, according to the

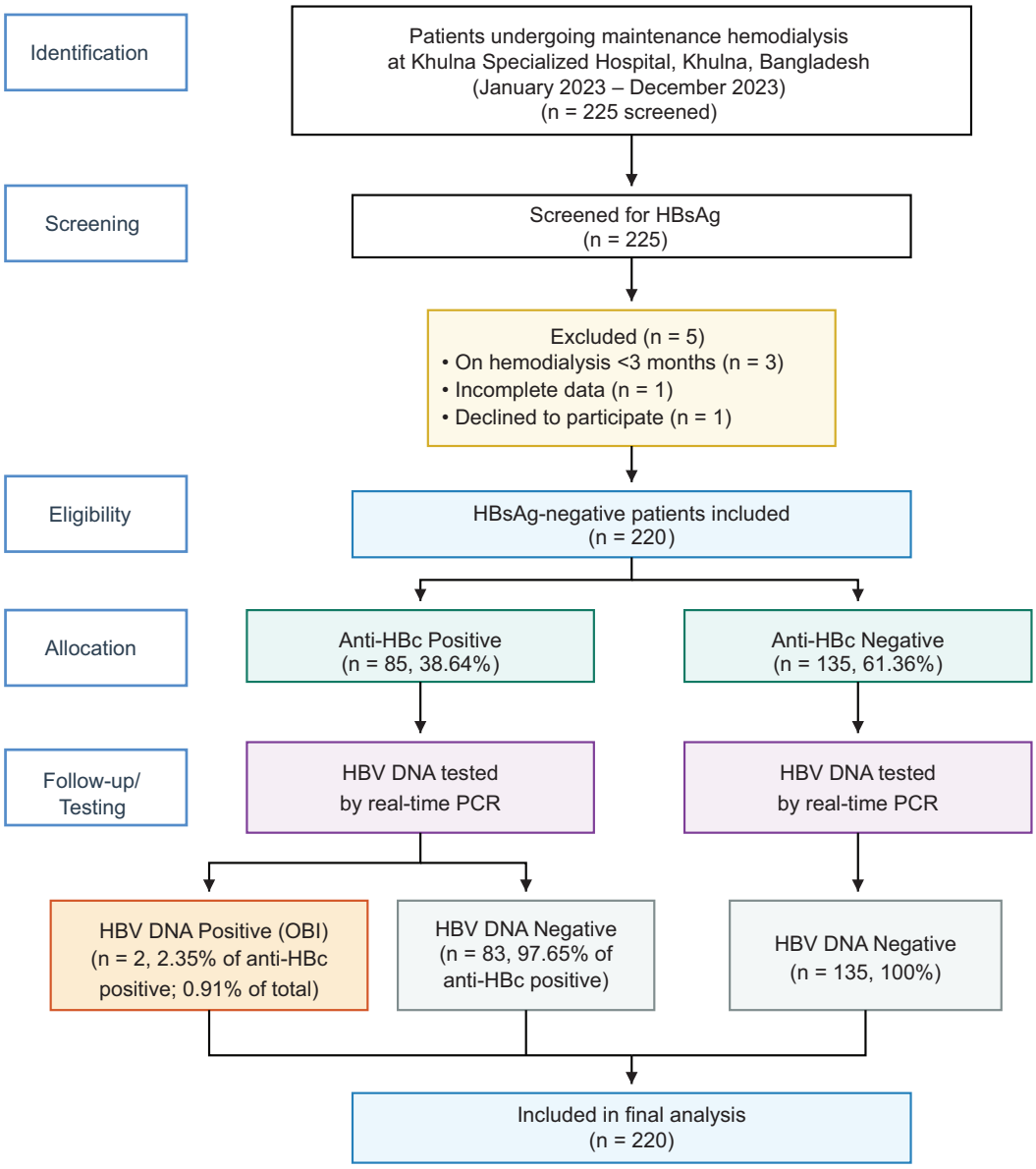
manufacturer's protocol. Qualitative detection of HBV DNA was performed using a real-time PCR system (QIAGEN, Germany).

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 31.0 (SPSS Inc., Chicago, IL, USA). Descriptive and inferential statistics were used to summarize baseline characteristics, and appropriate inferential tests were applied where relevant. A *p*-value of <0.05 was considered statistically significant.

Results

A total of 220 HBsAg-negative hemodialysis patients were included in this study, with a mean age of 47.87 ± SD 13.46. Of these, 67% were male, and 33% were female. All patients were receiving hemodialysis twice weekly for four hours per session and had completed hepatitis B vaccination according to the standard schedule at 0, 1, and 2 months.



HBsAg: Hepatitis B surface antigen; Anti-HBc: Antibody to hepatitis B core antigen; HBV DNA: Hepatitis B virus deoxyribonucleic acid; OBI: Occult hepatitis B infection; PCR: Polymerase chain reaction.

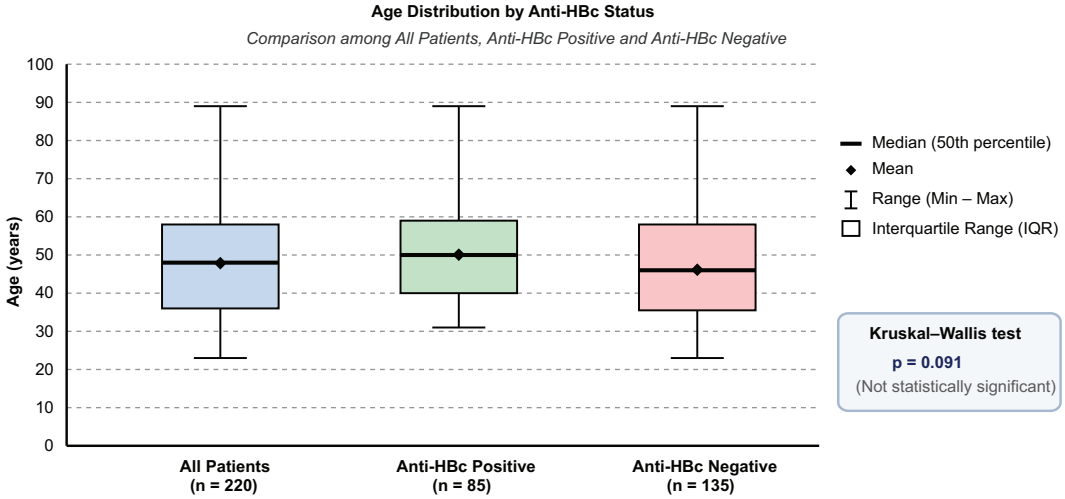
Figure 1: *CONSORT style flow chart of the study*

Serological findings

Anti-HBc antibodies were detected in 85 (39%) of the 220 participants, while 135 (61%) were tested negative. The distribution of Anti-HBc serostatus by age among study participants was given in (Figure 2). Among anti-HBc–positive patients, 60 (71%) were male, and 25 (29%) were female. (Figure 2)

HBV DNA detection

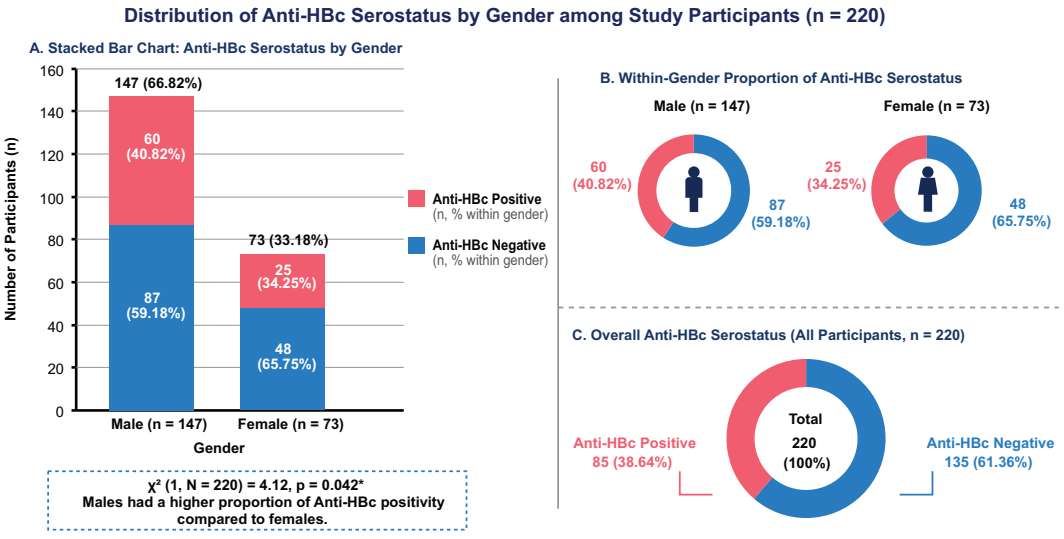
HBV DNA was detected in 2 (0.9%) of the 220 HBsAg-negative patients. Both HBV DNA–positive cases were male and anti-HBc–positive, indicating that 2.35% of anti-HBc–positive individuals had OBI. No HBV DNA was detected among anti-HBc–negative patients.



	All Patients (n = 220)	Anti-HBc Positive (n = 85)	Anti-HBc Negative (n = 135)
Mean ± SD (years)	47.87 ± 13.46	50.08 ± 12.74	47.00 ± 13.73
Median (years)	48	50	46
Range (Min – Max)	23 – 89	31 – 89	23 – 89

SD: Standard Deviation; Min: Minimum; Max: Maximum

Figure 2: *Age Distribution and Statistical Summary by Anti-HBc Status*



Gender	Anti-HBc Negative		Anti-HBc Positive		Total	
	n	% within gender	n	% within gender	n	% within gender
Male	87	59.18%	60	40.82%	147	66.82%
Female	48	65.75%	25	34.25%	73	33.18%
Total	**135**	**61.36%**	**85**	**38.64%**	**220**	**100%**

Anti-HBc: Antibody to hepatitis B core antigen; n: number; %: percentage

Figure 3: *Distribution of Anti-HBc serostatus by gender among study participants (n = 220).*

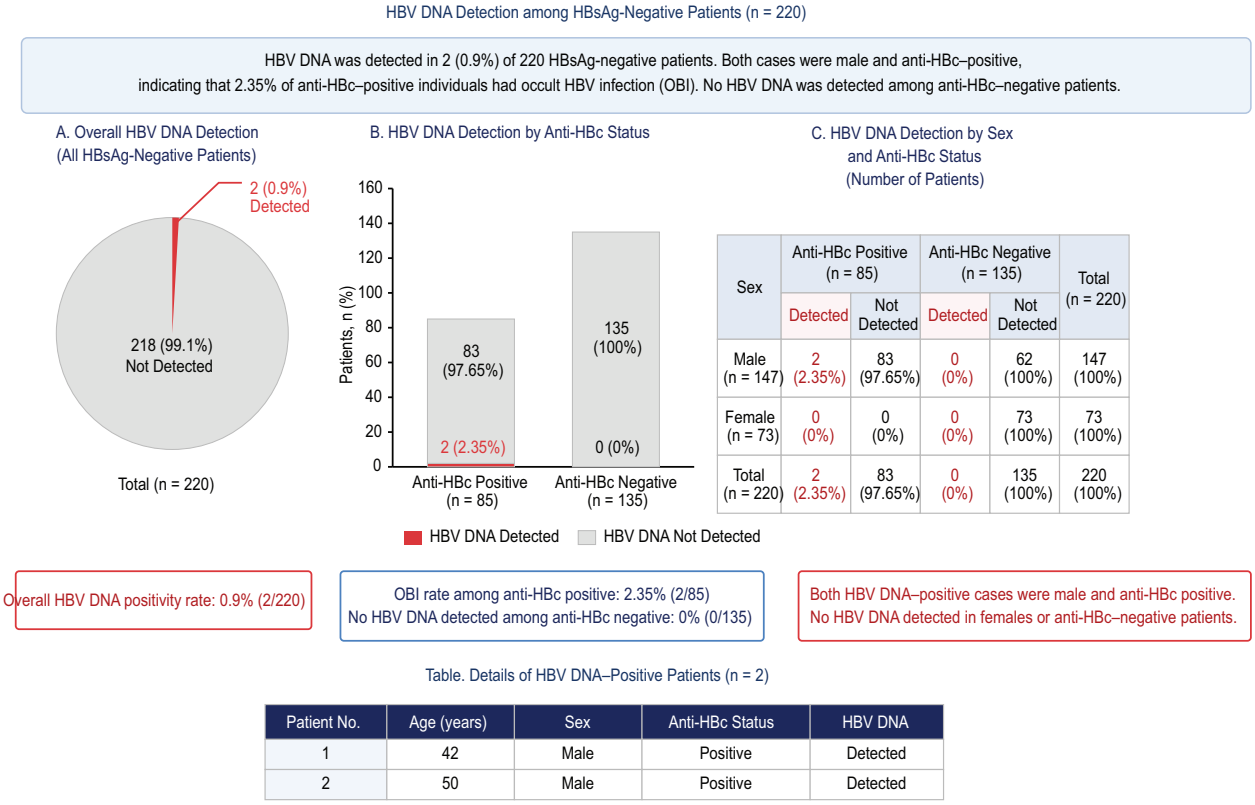


Table. Details of HBV DNA–Positive Patients (n = 2)

Patient No.	Age (years)	Sex	Anti-HBc Status	HBV DNA
1	42	Male	Positive	Detected
2	50	Male	Positive	Detected

HBsAg: Hepatitis B surface antigen; Anti-HBc: Antibody to hepatitis B core antigen; HBV DNA: Hepatitis B virus deoxyribonucleic acid; OBI: Occult hepatitis B infection.

Figure 4: *HBV DNA detection among HBsAg negative patients (n=220)*

Discussion

In an HBsAg-negative individual, the presence of anti-HBc indicates one of several possibilities: the window period of acute infection, a past infection without protective anti-HBs antibodies, or chronic infection with anti-HBc alone. In a simple way, HBsAg-negative and anti-HBc-positive indicated the state of the late phase of HBV infection or occult HBV status. When anti-HBc appears during the core window phase, it usually persists only for a few weeks, but in some individuals it can remain detectable for years. In certain cases, this pattern may also be explained by atypical infections, such as HBV mutants or patients with circulating HBV DNA despite undetectable HBsAg[3].

As OBI is characterized by the detection of HBV DNA in blood and /or within hepatocytes in the absence of HBsAg with or without detection of Anti–HBc antibody[10]. Detection HBV DNA in serum or hepatocytes is the gold standard for the diagnosis of occult hepatitis B virus (OBI). Liver biopsy is essential for the diagnosis of seronegative OBI, but this is not done routinely. This is an invasive procedure and carries a higher risk for complications[14,15].

In our study, only two cases of seropositive OBI were found (that means Anti-HBc positive and HBV DNA positive), but no seronegative OBI was found (that means Anti- HBc negative but HBV DNA positive)

Another important finding is a substantial proportion of patients having positive Anti –HBc but negative HBV DNA.

Occult hepatitis B virus infection is commonly detected in patients with isolated anti-HBc positive (HBs Ag negative and anti-HBc positive), though there is a little other probability of Anti–HBc positive.

The clinical importance of OBI is not only its transmission risk during hemodialysis but also its association with the progression of liver fibrosis and hepatocellular carcinoma, especially in immunocompromised patients. In this context, some researchers consider Anti–HBc alone, especially in the absence of HBsAg as one of the potential or surrogate marker for OBI and warrants further evaluation[16,17].

Most of the hemodialysis patients receive multiple blood transfusions, so that they are at high risk for acquiring HBV and occult hepatitis B virus infection[18].

In this study, 67% of the study population was male, and Anti-HBc positivity was more prevalent among males (70.59%) compared to females (29.41%). A study from Japan showed, the prevalence of Anti –HBc was higher in men than women[19].

This gender disparity aligns with existing literature, where males often show higher seroprevalence of HBV markers, possibly due to behavioral, hormonal, or immunological differences influencing HBV susceptibility and clearance[20,21].

The mean age of our study population was 47.87 ± 13.46. Population of Other studies had similar age ranges. For Example, a study from India had mean age 50.02 years[22].

The mean age of Anti-HBc positive patients (50.08 years) was slightly higher than that of Anti-HBc negative patients (47.00 years), although this difference was not statistically significant ($p = 0.091$). Both groups showed a wide age range, with Anti-HBc negative patients ranging from 23 to 89 years and positives from 31 to 89 years. The risk of Anti- HBc positivity was high in older people. This finding was may be due to prolong exposure to HBV infection in proportion to the length of time on hemodialysis. These findings suggest that age may not be a strong factor influencing Anti-HBc positivity in this patient population.

The prevalence of occult HBV (OBI) varies widely in different geographical areas. Bangladesh belongs to prevalence of intermediate endemicity (2-8%) of HBV infection. So, the prevalence of OBI is relatively similar to the prevalence if HBV infection of that community or geographical region. In this present study showed that in studied HBsAg negative patients, the prevalence of Anti-HBc positive was 39% but rate Occult hepatitis B virus infection was 0.9% in our study. The prevalence of occult HBV infections present ranges from 0 % to 58 % among the patients in maintenance dialysis in different previous studies[23].

Ramezani *et al* showed in their study, prevalence of Anti HBc and occult hepatitis B in dialysis patients were 2% and 1% respectively[5]. Sood *et al* from India showed prevalence of Anti HBc was 4% and HBV DNA was 0% in their study[22]. A study from Japan stated, the prevalence of Anti -HBc was 20.6% and prevalence of OBI was 0.11% that comparable to previous reports to our study[19].

Another recent paper from intermediate endemic country of HBV reported the prevalence of Anti HBc antibody and OBI was 26.3% and 4.2% respectively[24].

On the other hand, Helaly GF et al reported higher prevalence of Occult HBV infection rate (32%) in their study[25].

The wide variation in the results of different studies like our study is due to differences in the prevalence of HBV infection in geographical areas, differences in the sensitivity of different molecular technique used in the studies in the detection HBV DNA, variation in the sample size of the studies, age and sex of the patients[26,27].

This study showed a low rate OBI in hemodialysis patients. It can be due to increased awareness regarding the transmission of HBV infection, more coverage of HBV vaccination to dialysis patients and periodic surveillance of HBV infection. Serological markers for HBV infection should be complemented with DNA testing to detect possible occult HBV infection (OBI).

Strength &Limitation: As our knowledge, this is the first study in our country regarding occult HBV infection in hemodialysis patients. A relatively small sample size was one of the limitations of our study. Another limitation of our study was the lack of anti-HBs status against HBV.

Implications for clinical practice and policy: Blood donor with anti HBc positive should be discarded. Anti–HBc alone should be considered as important marker for detecting OBI in hemodialysis patients.

Conclusion

The hemodialysis patients with OBI infection remain as a silent disease which may leads to severe consequences. HBsAg alone is not adequate test to detect HBV infection especially in dialysis patients. For diagnosis of OBI, HBV DNA testing should be done especially in high-risk patients, like kidney transplantation and hemodialysis. Future studies focusing on cost effective way of detecting OBI are warranted.

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