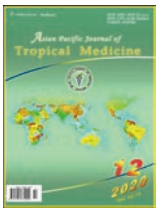

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Patterns of hepatitis B virus exposure and associated predictors in Vietnam: A cross-sectional study

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ABSTRACT

Objective: To examine the magnitude of isolated anti-HBc and other HBV serological patterns and associated predictors among adults seeking general health check-up at a large health center in Vietnam.

Methods: All 564 outpatients seeking general health check-up between January 2016 and December 2016 were asked to undertake HBV surface antigen, surface antibody, IgG and IgM core antibody (anti-HBc total), platelet counts, and liver function testing. An administered questionnaire was used to collect information regarding demography, in-house sources of infection, lifestyle, health condition and treatment, and HBV vaccination.

Results: Male gender (P=0.043), age (P=0.000), living in urban areas (P=0.040), HBV vaccination status (P=0.033), and ALT (P=0.040) were associated with isolated anti-HBc. HBV infection was associated with HBV vaccination status (P=0.001), ALT levels (P=0.010), AST levels (P=0.020), and platelet counts (P=0.007). Past/resolved HBV infection was associated with AST levels (P=0.005), ALT levels (P=0.014), and age (P=0.000).

Conclusions: Isolated anti-HBc is quite prevalent. Predictors of isolated anti-HBc include male gender, living in rural areas, and HBV non-vaccination. The prevalence of isolated anti-HBc also increases with age. To timely detect occult HBV infection and prevent transmission, anti-HBc testing should be included in the health check-up for high risk individuals and screening program where HBV nucleic acid test is not available. To prevent transmission, clinicians need to pay more attention on those who are at risk of having isolated anti-HBc and closely follow-up patients with isolated anti-HBc and educate them about the prevention of HBV infection.

KEYWORDS: HBV; Vietnam; Predictors; Isolated anti-HBc; Seroprevalence

1. Introduction

Hepatitis B virus (HBV) infection is a global public health problem. Although there has been a decrease in the prevalence of HBV infection worldwide due to expanded immunization, the number of people with chronic HBV infection is estimated to be 257 million[1]. In high endemic areas including Southeast Asia, the prevalence of HBV infection is over 8%[2,3]. In Vietnam, HBV prevalence ranges from 10% to 20% in the general population and is higher in the other high-risk groups such as chronic hemodialysis population and people with HIV/AIDS[4-7]. The control and prevention of HBV infection are mainly based on the New-born Universal Vaccination Program introduced in late 2003 and HBV surface antigen (HBsAg) screening for blood donors introduced in the 1990s[4]. However, there are still unsolved challenges that make HBV infection remains a major public health problem in Vietnam. Despite the reported high infant vaccination coverage rate (*i.e.* 93% in 2006 with unpublished surveys report that the rate has fluctuated since then), a decline in the burden of HBV infection can only be observed in the 2003 cohort onwards[4]. In addition,

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adverse events following immunization have resulted in fluctuations in vaccination coverage in recent years[8]. The use of HBsAg test alone may fail to detect all infections. Although highly sensitive HBsAg tests have been utilized, transmission may be detected from healthy blood donors due to the undetectable HBsAg in occult HBV infection (OBI)-a condition in which serum or liver HBV-DNA is persisted and detected in the absence of HBsAg[9], or during the seroconversion period[10]. In addition, in some individuals, HBsAg and HBV surface antibody (anti-HBs) are negative while HBV core antibody (anti-HBc) is positive. This condition is defined as isolated anti-HBc and is not an infrequent serological pattern[11,12]. Isolated anti-HBc is a clinical problem as it can be a serological marker for OBI[13]. However, information on the local burden of isolated anti-HBc is scarce[4]. There is also no local guideline for the management of isolated anti-HBc. We aimed to examine the magnitude of isolated anti-HBc and other different serological patterns of HBV exposure in people seeking general health check-up at one of the largest outpatient clinics in Vietnam. We also aimed to identify predictors for different patterns of HBV.

2. Patients and methods

2.1. Study design

A cross-sessional study was conducted at MEDIC Medical Center in Ho Chi Minh City between January 2016 and December 2016. MEDIC, established in 1990, is a system of several accredited ISO 15189:2012 laboratories and outpatient clinics across Vietnam, Laos and Cambodia[14,15]. In Vietnam, MEDIC is among the leading medical centers that provide both laboratory services and outpatient care to all residents in Vietnam, especially those from southern Vietnam including the Mekong Delta[14,15].

During the study period, all outpatients seeking general health check-up were invited to participate in the study. To the best of our knowledge, in Vietnam, people seek general health check-up voluntarily or upon requested by their employers. To ensure the validity of laboratory findings associated with HBV infection, the inclusion criteria included being $\geqslant$18 years-old and not having hepatitis C virus (HCV) and/or human immunodeficiency virus (HIV) infection, hepatic failure, cirrhosis and hepatocellular carcinoma. HCV infection and liver condition status were examined by the same researcher who is a qualified hepatologist based on the assessment of patients' anti-HCV test results and clinical findings, while HIV infection status was assessed based on self-report. The study participants did not undertake any anti-viral medications and primarily seek other health services rather than general health check-up.

2.2. Informed consent and ethnical approval

All study participants provided written informed consent. The study procedure was performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by our local Ethics Committee (Reference No. 19/2016/NCKH-YTHH).

2.3. Data collection

Information regarding demography (*e.g.* age, sex, height, weight, living location, and job), in-house sources of infection (*e.g.* having HBV infected parent (s), sibling (s) or sexual partner (s), life-styles (*e.g.* unprotected sexual contact; injecting drug use; shared use of razor blades and toothbrushes; tattooing; and acupuncture with reused needles), treatment history (*e.g.* hemodialysis, surgery, and blood transfusion), pregnancy status, and HBV vaccination was collected by the same researcher using an administered questionnaire. Having HBV vaccination was defined as completing a full vaccination course. To validate the information of self-reported HBV vaccination status, HBV vaccination records were reviewed. When records were not available, patients who reported a completed vaccination course were asked to provide the month and place of vaccination and the number of doses. Study participants were contacted for verification if information was found to be invalid during the data cleaning process.

2.4. Laboratory tests

All study participants underwent serologic screening including HBsAg (Elecsys HBsAg][assay, Roche Diagnostics GmbH, Mannheim, Germany), IgG and IgM anti-HBc (anti-HBc total) (Elecsys anti-HBc][assay, Roche Diagnostics GmbH, Mannheim, Germany) and anti-HBs (Elecsys anti-HBs][assay, Roche Diagnostics GmbH, Mannheim, Germany) in accordance with the manufacturer's instructions. Other laboratory tests include platelet counts [reference range: (130-400)$\times 10^3$/μL], aspartate aminotransferase (AST, reference range <35 IU/mL), alanine aminotransferase (ALT, reference range <30 IU/mL), and gamma gluatamyl transerase (GGT, reference range <50 IU/mL). Patients with documented positive HBV serology results were asked to undergo the same process to ensure the validity of the screening result.

In the present study, the patterns of HBV exposure were classified into three groups, including (1) HBsAg negative and anti-HBc total negative (HBV non-infection), (2) HBsAg positive and anti-HBc total positive (HBV infection), (3) HBsAg negative and antiHBc total positive. Anti-HBs status was used to further classify the third

Table 1. Trend analysis on the prevalence of demographic and laboratory characteristics and source of infection among different patterns of HBV exposure.

Characteristics	HBsAg (-) and anti-HBc total (-) (HBV non-infection; *n*=234)	HBsAg (+) and anti-HBc total (+) (HBV infection; *n*=106)	HBsAg (-), anti-HBs (+) and anti-HBc total (+) (Past/ resolved infection; *n*=187)	HBsAg (-), anti-HBs (-) and anti-HBc total (+) (isolated anti-HBc; *n*=37)	*P* value	Statistics
Demographics [*n* (%)]						
Male	99 (42.3)	67 (63.2)	91 (48.7)	23 (62.2)	0.039$^{\wedge}$	4.3$^{\$}$
White-collar workers	66 (28.2)	20 (18.9)	27 (14.4)	8 (21.6)	0.003$^{\wedge}$	8.7$^{\$}$
Living in urban area	78 (33.3)	25 (23.6)	45 (24.1)	5 (13.5)	0.004$^{\wedge}$	8.2$^{\$}$
Having HBV vaccination	68 (29.1)	1 (0.9)	41 (21.9)	3 (8.1)	0.006$^{\wedge}$	7.7$^{\$}$
Age (mean±SD, years)	37.2±12.8^{a}	41.1±13.6^{ad}	45.2±12.9^{bc}	45.6±13.0^{cd}	<0.001$^{\triangle}$	14.4*
Laboratory						
Platelet (mean±SD, $\times 10^3$/μL)	254±58^{a}	226±61^{b}	255±60^{a}	264±62^{a}	0.001$^{\triangle}$	7.2*
AST [(median, IQR), IU/mL)]	22 (18, 28)^{x}	33 (25, 53)^{y}	23 (19, 30)^{x}	23 (19, 29)^{x}	<0.001$^{\&}$	4.9*
ALT [(median, IQR), IU/mL)]	21 (14, 35)^{x}	35 (22, 78)^{y}	24 (16, 37)^{x}	23 (17, 38)^{x}	<0.001$^{\&}$	9.7*
GGT [(median, IQR), IU/mL)]	26 (16, 54)^{x}	35 (18, 66)^{y}	33 (20, 59)^{x}	45 (22, 93)^{yx}	0.002$^{\&}$	5.6*
In-house sources of infection [*n* (%)]						
Having HBV infected parent (s)	8 (3.4)	15 (14.2)	5 (2.7)	1 (2.7)	0.650$^{\wedge}$	0.2$^{\$}$
Having HBV infected sexual partner (s)	8 (3.4)	13 (12.3)	5 (2.7)	1 (2.7)	0.653$^{\wedge}$	0.2$^{\$}$
Having HBV infected sibling (s)	2 (0.9)	15 (14.2)	7 (3.7)	1 (2.7)	0.237$^{\wedge}$	1.4$^{\$}$

$^{\wedge}$*Chi*-square for trend. $^{\triangle}$One way ANOVA. $^{\&}$Kruskal-Wallis test. $^{\$}$*Chi*-squared value. **F* value. $^{a\text{-}d}$Tukey post-hoc analysis shows significant difference between groups without a common superscript letter in the same row. $^{x\text{-}y}$Dunn Bonferroni *post hoc* analysis shows significant difference between groups without a common superscript letter in the same row.

group into two sub-groups including (3a) HBsAg negative, anti-HBs positive and anti-HBc total positive (past/resolved infection) and (3b) HBsAg negative, anti-HBs negative and anti-HBc total positive. The latter sub-group was defined as isolated anti-HBc[12]. For comparison purposes, we also calculated the prevalence of isolated anti-HBc when isolated anti-HBc was defined as HBsAg (-) and anti-HBc total (+) regardless of anti-HBs status.

2.5. Statistical analysis

Statistical Package for the Social Sciences version 25 (IBM) was used to manage and analyze the data. Continuous variables with normal distribution were presented as mean±SD, while non-normal variables were reported as median [interquartile range (IQR)]. Categorical variables were presented as number and percentages. One-way analysis of variance was used to compare continuous data with normal distribution between groups, while Kruskal-Wallis Test was used for non-normal variables. Turkey and Dunn Bonferroni were used to determine *P* value in *post hoc* tests. *Chi*-square for trend test was utilized to examine the association between categorical data. A multinomial logistic regression model was developed to examine predictors for the patterns of HBV exposure. Independent variables that were statistically significant in univariate analysis were entered into the multinomial logistic regression model. To prevent residual confounding effect, all continuous variables including age, AST, ALT, GGT and platelet were not dichotomized in the analysis. The significance level was set at $P \leqslant 0.05$.

3. Results

The recruitment rate was 100% resulting in 564 patients in the study, of whom 282 (50.0%) were male and the mean age was (41.1±13.4) years. One hundred and six patients (18.8%, 95% *CI:* 15.8%-22.2%) were HBsAg positive, 280 (49.6%) were anti-HBs positive, and 332 (58.9%) were anti-HBc positive. The patterns of HBV exposure included 234 (41.5%, 95% *CI:* 37.5%-45.6%) patients without HBV infection, 106 (18.8%, 95% *CI:* 15.8%-22.2%) with HBV infection, 187 (33.2%, 95% *CI:* 29.4%-37.1%) with past/ resolved infection, and 37 (6.6%, 95% *CI:* 4.8%-8.9%) with isolated anti-HBc. If isolated anti-HBc is defined as HBsAg (-) and anti-HBc total (+) regardless of anti-HBs status, the prevalence of isolated anti-HBc was 39.7% (224/564, 95% *CI:* 35.7%-43.9%) (Table 1).

The mean age of 37 patients with isolated anti-HBc defined as HBsAg negative, anti-HBs negative and anti-HBc total positive was (45.6±13.0) years, of whom male and having HBV vaccination was 23 (62.2%) and 3 (8.1%), respectively. In-house sources of infection (3/37, 8.1%), having tattooing or blood transfusion (0.0%), having unprotected sexual contact (3/37, 8.1%), and surgery (5/37, 13.5%) were documented. Increased AST and ALT were record in 16.2% (6/37) and 21.6% (8/37) of patients, respectively.

Among 106 patients with HBV infection, male and having HBV vaccination was 67 (63.2%) and 1 (0.9%), respectively. The mean age of these patients was (41.1±13.6) years. In-house sources of infection (43/106, 40.6%), having tattooing (19/106, 17.9%), blood transfusion (0.0%), unprotected sexual contact (2/106, 1.9%), and surgery (11/106, 10.4%) were documented. Increased AST and

Table 2. Multinominal logistic regression analysis for predictors of patterns of HBV exposure.

Risk factors	HBsAg (+) and anti-HBc total (+) (HBV infection; *n*=106)		HBsAg (-), anti-HBs (+) and anti-HBc total (+) (past/resolved infection; *n*=187)		HBsAg (-), anti-HBs (-) and anti-HBc total (+) (isolated anti-HBc; *n*=37)	
	P value	Adjusted *OR* (95% *CI*)	*P* value	Adjusted *OR* (95% *CI*)	*P* value	Adjusted *OR* (95% *CI*)
Age	0.066	-	0.000	1.047 (1.029-1.065)	0.000	1.054 (1.024-1.085)
Male (*vs.* female)	0.087	-	0.229	-	0.043	2.322 (1.028-5.243)
White-collar workers (*vs.* blue-collar workers)	0.439	-	0.150	-	0.424	
Living in urban area (*vs.* living in rural area)	0.262	-	0.760	-	0.040	0.335 (0.118-0.953)
Having HBV vaccination (*vs.* no vaccination)	0.001	0.033 (0.004-0.240)	0.775	-	0.033	0.256 (0.073-0.894)
ALT (IU/mL, reference range <30)	0.010	1.014 (1.003-1.025)	0.014	1.015 (1.003 – 1.027)	0.040	1.018 (1.001-1.036)
AST (IU/mL, reference range <35)	0.020	0.991 (0.984-0.999)	0.005	0.969 (0.948 – 0.991)	0.131	-
GGT (IU/mL, reference range <50)	0.316	-	0.197	-	0.610	-
Platelet ($\times 10^3$/μL, reference range: 130–400)	0.007	0.993 (0.989-0.998)	0.628	-	0.464	-

Reference group: HBsAg (-) and anti-HBc total (-) (HBV non-infection).

ALT were record in 37.7% (40/106) and 42.5% (45/106) of patients, respectively.

One hundred and eighty-seven patients with past/resolved infection had a mean age of (45.2±12.9) years, of whom male and having HBV vaccination was 91 (48.7%) and 41 (21.9%), respectively. In-house sources of infection (17/187, 9.1%), having tattooing (20/187, 10.7%), blood transfusion (4/187, 2.1%), unprotected sexual contact (0.0%), and surgery (30/187, 16.0%) were documented. Increased AST and ALT were record in 10.2% (19/187) and 20.3% (38/187) of patients, respectively.

3.1. Demographic characteristics

The proportions of male gender (*P*=0.039), white-collar workers (*P*=0.003), patients living in urban area (*P*=0.004), and patients having HBV vaccination (*P*=0.006) were statistically different between groups of patterns of HBV exposure (Table 1). The mean age was statistically different between groups (*P*=0.000).

3.2. In-house sources of infection

There was no statistically significant linear trend between patterns of HBV exposure and three in-house sources of infection.

3.3. Life-style characteristics and treatment history

There was no significant association between documented risk factors and patterns of HBV exposure (data not shown). Univariate analysis of pregnancy status, injecting drug use, shared use of razor blades and toothbrushes, acupuncture with reused needles, and hemodialysis could not be performed because no participants reported having had these risk factors.

3.4. Laboratory characteristics

The mean platelet counts (*P*=0.001) and the median AST (*P*=0.000), ALT (*P*=0.000), and GGT (*P*=0.002) levels were statistically different between groups.

3.5. Model for the prediction of patterns of HBV exposure

Male gender (*P*=0.043, adjusted *OR*=2.322, 95% *CI:* 1.028-5.243), age (*P*=0.000, adjusted *OR*=1.054, 95% *CI:* 1.024-1.085), living in urban areas (*P*=0.040, adjusted *OR*=0.335, 95% *CI:* 0.118-0.953), HBV vaccination status (*P*=0.033, adjusted *OR*=0.256, 95% *CI:* 0.073-0.894), and ALT (*P*=0.040, adjusted *OR*=1.018, 95% *CI:* 1.001-1.036) were associated with having isolated anti-HBc defined as HBsAg negative, anti-HBs negative and anti-HBc total positive. HBV infection was associated with ALT levels (*P*=0.010, adjusted *OR*=1.014, 95% *CI:* 1.003-1.025), AST levels (*P*=0.020, adjusted *OR*=0.991, 95% *CI:* 0.984-0.999), platelet counts (*P*=0.007, adjusted *OR*=0.993, 95% *CI:* 0.989-0.998), and HBV vaccination status (*P*=0.001, adjusted *OR*=0.033, 95% *CI:* 0.004-0.240). Past/resolved HBV infection was associated with age (*P*=0.000, adjusted *OR*=1.047, 95% *CI:* 1.029-1.065), ALT levels (*P*=0.014, adjusted *OR*=1.015, 95% *CI:* 1.003-1.027), and AST levels (*P*=0.005, adjusted *OR*=0.969, 95% *CI:* 0.948-0.991). Patterns of HBV exposure were not associated with job and GGT (Table 2).

4. Discussion

The prevalence of HBV infection in our study is higher than that of the WHO Western Pacific Region (6.2%), WHO African Region (6.1%), WHO Eastern Mediterranean Region (3.3%), and WHO European Region (1.6%)[1]. In Asia, a recent systematic review and

meta-analysis has identified that the pooled prevalence estimate of HBV infection in the general population of China is 6.9% (95% *CI*: 5.8%-8.0%)[16], which is smaller than in Vietnam. Similarly, the rate is higher than that of Thailand (5.1%, 95% *CI*: 4.3%-6.0%) [17] and Singapore (3.6%, 95% *CI*: 2.9%-4.2%)[18]. In Vietnam, the prevalence is similar to that of the members of the general community[4,19]. HBsAg testing is the most common screening method for HBV. However, despite all efforts including the use of a highly sensitive HBsAg test, HBV transmission still occurs from apparently healthy blood donors because HBsAg may not be detected during the window period and in OBI[10]. Therefore, it is suggested that anti-HBc testing should be concurrently performed to increase the probability of detecting HBV infections[20]. In a subset of anti-HBc carriers, isolated anti-HBc has increasingly been of clinical interest because it can be a serological marker for OBI[13]. Isolated anti-HBc can also be interpreted as acute, resolved, low level chronic infection, or false positive anti-HBc[13]. The prevalence of isolated anti-HBc varies in different populations worldwide ranging between 1% and 32%[13]. In Asia, studies conducted in Malaysia, Korea, and China identified the prevalence of isolated anti-HBC of 5%, 8.9%, and 11.9%, respectively[21-23]. In contrast, in Vietnam, only few studies provided data on anti-HBc and report on isolated anti-HBc which is strictly defined as HBsAg (-), anti-HBs (-) and anti-HBc total (+) is not available[4]. Isolated anti-HBc is commonly detected in intravenous drug users, HIV-infected patients, HBV and HCV co-infected patients, and pregnant women even though the reason remains unclear[24]. In light of this, our isolated anti-HBc prevalence is considerably high provided that our study participants were neither injecting drug users and pregnant women nor have HCV or HIV infection. For comparison purposes, if isolated anti-HBc is defined as HBsAg (-) and anti-HBc total (+) regardless of anti-HBs status, our rate is comparable with the high rate reported from a large population-based study conducted in rural Vietnam (42%, 95% *CI*: 39.4%-45.0%)[25]. Isolated anti-HBc can highly reflect OBI in high-risk populations including hemodialysis or HIV-infected patients but may not presume OBI in low-risk group like blood donors[26]. The use of nucleic acid testing (NAT) for HBV DNA greatly enhances the accuracy in identifying OBI cases[25]. However, NAT is expensive and may not pick up mutated virus, and the technology may not be feasible in low-resource settings[25]. To achieve maximal safety, developed countries like Japan has further added anti-HBs testing to their complex screening algorithm and discarded all units with low anti-HBc and anti-HBs titers because these units are associated with low-level viremia[27]. It is recommended that HBV screening strategy should be decided based on local epidemiology, estimate of the infectious risk, and resources[28]. Given HBV infection is highly endemic in Vietnam, anti-HBc testing should be included in the blood screening program where NAT is not available and offered to those seeking HBV screening as part of their general health check-up to detect isolated anti-HBc. Isolated anti-HBc individuals can subsequently undertake HBV-DNA testing to detect OBI.

Information on the characteristics of people with isolated anti-HBc and associated predictors is scarce. We found that protective factors for isolated anti-HBc include female gender, living in urban area, and having HBV vaccination. Our finding regarding the association between gender and this pattern is consistent with another large study conducted in Germany and is probably due to a higher frequency of chronic HBV infection in the male group of the underlining population[29,30]. Having a history of HBV vaccination decreased the risk of acquiring HBV infection including isolated anti-HBc provided that this pattern is a marker of HBV infection. This finding is not surprised as the effectiveness of HBV vaccine in preventing HBV infection is well documented[31]. However, HBV vaccination rate in rural area in Vietnam is suboptimal compared with urban area, which in turn makes living in rural area a risk for having isolated anti-HBc[30]. Similar to another study[32], we also found that the prevalence of isolated anti-HBc increased with age. In addition, we found an association between changes in ALT and isolated anti-HBc. However, a recent study found that ALT levels in patients with isolated anti-HBc were not different compared with the uninfected people and people developing immune due to natural infection[9]. Therefore, more robust studies are needed to validate the association between liver enzymes and isolated anti-HBc.

Anti-HBc positive is the main indicator for past HBV infection which may subsequently resolve, especially in high endemic countries like Vietnam[4]. We found that the age of HBV past/resolved infection group was statistically older than that of the non-infection group which is consistent with other local study[30]. We also found that platelet counts are inversely associated with HBV infection which is consistent with other reports[33]. Similar to other studies, the ALT levels of our HBV non-infection group were statistically lower than those of HBV infection and past/resolved infection group[19]. This can be explained by the elevation or fluctuation of ALT levels in chronic HBV infection and a slow decrease in ALT levels in resolved infection[34]. An inverse association between AST levels and HBV infection and past/resolved infection group has been found in our study and is of minimal clinical importance. Indeed, it is well documented that AST is less specific for liver disease[35]. Although history of acupuncture, reuse of syringes, and sharing of razors were found to be associated with HBV infection[19], the association between patterns of HBV exposure and life-style risk factors and treatment history was not identified in our study which can be due to the homogeneity of the

study population.

To the best of our knowledge, there are no studies to examine the characteristics and predictors of isolated anti-HBc in Vietnam. Our study would add to the body of knowledge about isolated anti-HBc in Vietnam and comparable countries. However, there are some limitations preventing us from further examining isolated anti-HBc individuals. HBV-DNA testing was not performed due to financial constraints, and thus we were unable to detect occult HBV infection in this group. We could not follow-up patients with isolated anti-HBc to differentiate between acute, resolved, low level chronic infection and false positive anti-HBc due to the nature of a cross-sectional study. Yet we believe that false positive anti-HBc is negligible because the study clinic is an accredited ISO 15189:2012 laboratory[14]. Although the study clinic provides health services to patients across Vietnam, the study population may not be a representative of all patients seeking regular health check-up. However, in addition to the recruitment rate of 100%, our findings are consistent with other studies and are relevant for improving the prevention and control of HBV infection.

In conclusion, the findings confirm that isolated anti-HBc is prevalent. Predictors of isolated anti-HBc include male gender, living in rural areas, and HBV non-vaccination. The prevalence of isolated anti-HBc also increases with age. To timely detect occult HBV infection and prevent its transmission, anti-HBc testing should be included in the health check-up for high risk individuals and the screening program where HBV NAT is not available. Clinicians need to pay more attention on those who are at risk of having isolated anti-HBc and closely follow-up patients with isolated anti-HBc and educate them about the prevention of HBV infection. Further large-scale epidemiological studies on isolated anti-HBc and occult HBV infection are required to provide essential information for planning HBV-related public health services and developing guideline for the management of isolated anti-HBc in Vietnam and comparable countries.

Conflict of interest statement

We declare that we have no conflict of interest.

Authors' contributions

MCD and PVDL developed conception of the work. PVDL, OKNP, HDTP, TBN, and HTP collected data. MCD, OKNP, HDTP performed the analysis and interpretation. MCD, OKNP, HDTP, TBN, and HTP drafted and critically revised the manuscript as well as approved the final version to be published.

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