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Original Article

Association of Routine Hepatitis B Vaccination and Other Effective Factors with Hepatitis B Virus Infection: 25 Years Since the Introduction of National Hepatitis B Vaccination in Iran

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What's Known

- The epidemiology of hepatitis B virus (HBV) infection in the pre-vaccine era has been studied widely, but few studies have been conducted since the introduction of HBV immunization.
- Different studies and countries have reported various factors affecting the morbidity and prevalence of the disease.

What's New

- This is the first study in Iran to investigate the factors associated with HBV infection, 25 years since the launch of national HBV immunization.
- National HBV immunization has reduced hepatitis B infection and the effects of its risk factors such as a family history of hepatitis B.

Abstract

Background: One of the main health problems in the world is hepatitis B virus (HBV) infection. Vaccination and other factors can affect HBV infection. As various effective factors have been reported in different regions and studies, this study aimed to investigate the association between HBV infection and routine vaccination and other effective factors 25 years since the launch of the national vaccination program in Iran.
Methods: This cross-sectional study, conducted in 2017 in Shiraz (Iran), investigated factors such as demographic variables such as gender, education, and occupation, vaccination status, and the potential risk factors for HBV infection. Hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antibody (HBc Ab) tests were performed to determine HBV infection status. The data were analyzed using R software (version 3.5.2), using multivariate logistic regressions and machine learning methods. The level of significance was considered below 0.05.
Results: A total of 2720 individuals were enrolled in the study (194 cases with HBV infection). Based on the logistic regression analyses, factors such as a family history of the disease (OR=2.53, $P<0.001$), vaccination (OR=0.57, P=0.004), a history of high-risk behaviors (OR=1.48, P=0.022), and occupation (OR=1.80, P=0.035) were significantly associated with HBV infection. Based on the conditional tree method, a family history of infection ($P<0.001$) and vaccination (P=0.023) were two important factors in classifying individuals for HBV infection.
Conclusion: Based on the different methods applied in this study, HBV infection was affected by factors such as a family history of the disease, national HBV vaccination, and occupation. It appears that HBV vaccination, launched by the Iranian Ministry of Health and Medical Education in 1993, has reduced HBV infection.

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Keywords ● Hepatitis B ● Risk factors ● Vaccination ● Logistic models ● Machine learning

Introduction

Hepatitis B is a viral infection and one of the main health problems in the world.[1] The prevalence of Hepatitis B virus (HBV) varies across different countries and regions, and this virus can increase the risk of cirrhosis and hepatocellular carcinoma.[2-5] Most cases of HBV infection have been reported from Asia, the Middle East, and Africa.[6] In countries with low socioeconomic status or poor health conditions, it appears that the majority of cases are transmitted from mother to child and happen in young children. The possibility of chronic HBV infection is greater in those infected in the neonatal period or childhood,[7] and about 25% of individuals with chronic infection die as a consequence.[6]

Vaccination is an essential way of controlling and preventing the transmission of HBV infection.[8] The mass vaccination of infants and children in the context of the Expanded Program on Immunization (EPI) was recommended by the World Health Organization in 1991.[9, 10] The complications of HBV infection may not be treated at the end stages, but HBV vaccination, currently implemented in many countries, can reduce the incidence and mortality of this infection.[11, 12] It has been shown that immunization against HBV within the first 24 hours of life and completing three doses during infancy and childhood play an important role in preventing HBV infection.[13]

Based on the results of previous studies, various factors such as high-risk sexual behaviors, intravenous illicit drug use,[14] a family history of the disease,[15] education, and socioeconomic status[16] can be associated with HBV infection. The results of a study in Pakistan showed that household contact; sexual contact; and a history of blood transfusion and its components, surgery and dental works were the main risk factors for the increased prevalence of HBV infection.[17]

Machine learning has been used for the prediction and classification of various aspects of HBV infection.[18-20] For instance, a previous investigation employed this modality as a decision-support system to enhance the stage diagnosis performance of HBV.[18] Various machine learning methods are currently in use for data classification.[19] Such methods are drawn upon in the fields of statistics, computer science, and artificial intelligence by their ability to create algorithms capable of data-based classification and prediction.[21]

The epidemiology of HBV infection in the pre-vaccine era has been investigated extensively, but only a few studies have been conducted since the introduction of HBV vaccination.[22] Awareness of the natural history and factors influencing the progression of HBV infection can be helpful in its management and treatment.

Previous research has shown various factors affecting the morbidity and prevalence of HBV infection in different countries.[18-20] In Iran, the national HBV immunization program was launched by the Iranian Ministry of Health and Medical Education in 1993.[23] Nevertheless, given the current dearth of data on HBV infection and its associated factors since the implementation of the aforementioned immunization program in Iran, we utilized logistic regressions and machine learning methods to explore the association of HBV infection with routine vaccination and other effective factors.

Patients and Methods

Study Population

The current cross-sectional study, conducted in Shiraz (Iran), evaluated 2720 individuals for HBV infection and the factors affecting its incidence, especially national HBV immunization.

This study was approved by the Research Ethics Committee of Shiraz University of Medical Sciences (Ethics Code: IR.SUMS.REC. 1397. 437). Data were collected through data-collection forms and blood sampling by trained interviewers and laboratory staff, correspondingly.

According to the studies used by the Centers for Disease Control and Prevention (CDC),[24] the disease rates in vaccinated and unvaccinated individuals were 4.1% and 10.7%, respectively. Therefore, according to the following formula at a 95% confidence interval (CI) and a power of 90%, we estimated a required sample size of at least 2258 individuals.

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 \left(\frac{\widetilde{p_1}\widetilde{q_1}}{n_1} + {\phi_0}^2 \frac{\widetilde{p_2}\widetilde{q_2}}{n_2}\right)}{\left(\hat{p}_1/\hat{p}_2 - \phi_0\right)^2}$$

In this formula, $\hat{p}_1$ and $\hat{p}_2$ represent disease rates in vaccinated and unvaccinated individuals, $\widetilde{p_1}$ and $\widetilde{q_2}$ represent the estimates of conditional maximum likelihood ratios, and Φ_0 is equal to $\widetilde{p_1}/\widetilde{p_2}$.[25]

The study samples were selected from individuals who referred to the only three health centers in Shiraz in 2017. Since the mandatory premarital screening tests in Iran require routine blood sampling for all individuals, we selected the study participants from among those undergoing mandatory screening to reduce problems relating to blood sampling. HBV infection tests are not routinely performed as a part of the mandatory premarital screening tests; consequently, after obtaining consent from the individuals, we took blood samples concurrently with the mandatory premarital screening tests.

Inclusion and Exclusion Criteria

On account of the year of the implementation of the infantile HBV vaccination program in Iran (1993) and also its high coverage (close to 100%),[23] vaccinated individuals were selected from among those born in 1994 and after and unvaccinated individuals from among those born in 1992 and before. Individuals who did not consent to participate in the study and those having a non-Iranian nationality were excluded from the study. In the unvaccinated group, individuals whom themselves received an HBV vaccine for any reason were excluded from the study.

Data Collection

Written informed consent was obtained from all the study participants after they had been given complete explanations about the goals and methods of the study. Thereafter, a blood sample of 4 mL was drawn from each person into an anticoagulant tube (Guangzhou Improve Medical Instruments Co, Ltd, Guangzhou, China) and transferred to the reference laboratory. For the transport of the samples, the serum samples were stored in a freezer (Sanyo, Japan) at −20 °C and then transferred to the lab with ice bags as soon as possible.

Definition of the Outcome

HBV infection status, determined via Hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antibody (HBc Ab) tests (Dia.Pro Diagnostic Bioprobes Srl, Italy), was considered to be the outcome. If either of these markers after blood sampling and serum separation was positive, the person was considered HBV infection positive.[22, 26, 27]

Associated Factors

Factors such as demographic variables, the potential risk factors of the disease, and a history of national HBV vaccination were investigated. In addition, a family history of HBV infection, comprising a history of HBV infection in father, mother, sister, brother, spouse, and child; high-risk behaviors such as tattoos, high-risk sexual contacts (e.g., extramarital sex), and intravenous illicit drug use; a history of surgery or dental work; and a history of the transfusion of blood or any blood product were measured.

Statistical Analysis

The data were analyzed with R software (version 3.5.2), via multivariate logistic regressions as a classical model and a recursive partitioning algorithm comprised of a conditional tree (using the "party" package), a conditional forest (using the "party" package), and a random forest (using the "randomForestSRC" package) as a new learning method. In the regression model, all the variables were analyzed using multivariate logistic regressions via the "Inter" method. The logistic regression and machine learning methods were utilized to achieve the following goals: to determine the factors associated with HBV infection, to predict HBV infection based on the related variables, and to determine the importance of these variables. The goodness of fit of the models was compared using accuracy and Brier score indices. In the conditional and random forest methods, the mean decrease Gini index was employed to measure the importance of variables in the classification, with a higher value of this index representing its higher importance.[28, 29] In all the tests, the level of significance was considered below 0.05.

The conditional tree divides the population based on the related factors, resulting in homogeneous subsets of the population. The advantages of the conditional tree method in comparison with regression models include its ability to deal with collinear variables and big data.[30, 31] This algorithm provides a P value useful to determine the level of confidence that can be obtained in each division.[32]

The conditional forest and the random forest are two types of forests applied to calculate the importance of variables.[30, 33] The random forest method was recently proposed for the prediction and selection of variables,[33] and its categorization can usually reduce the over-fitting problem often occurring in an individual decision tree.[18]

Results

The present study recruited 2720 individuals, of whom 194 (7.1%) were HBV infection positive. The mean age of the participants was 26.9±5.82years. Additionally, 85 (3.3%) cases had a history of HBV infection in their families, 1541 (56.6%) were women, and 1273 (46.8%) were vaccinated (table 1).

Factors Affecting HBV Infection

Concerning HBV infection, based on the logistic regression model, such variables as a family history of HBV infection (OR=2.53, P<0.001), a history of high-risk behaviors (OR=1.48, P=0.022), and occupation (OR=1.80, P=0.035, for the homemaker/self-employed categories) were risk factors, whereas national HBV vaccination was a protective factor (OR=0.57, P=0.004). In other words, those who had received the full doses of HBV vaccine in accordance with the national immunization program had a 43% lower chance of developing HBV infection and those who had a history of

Table 1: Distribution of sociodemographic characteristics among the study participants (N=2720)

Variable		Frequency (%)		
		Total	Vaccinated	Unvaccinated
Gender	Male	1184 (43.44)	309 (24.27)	872 (60.26)
	Female	1541 (56.56)	964 (75.73)	575 (39.74)
Education	Primary or middle school	190 (7.00)	55 (4.33)	134 (9.30)
	High school	154 (5.67)	89 (7.01)	65 (4.50)
	Diploma	970 (35.71)	558 (43.98)	409 (28.34)
	Academic/university	1402 (51.62)	567 (44.68)	835 (57.86)
Occupation	Self-employed	854 (33.44)	248 (20.91)	602 (44.13)
	Homemaker	585 (22.90)	359 (30.30)	226 (16.57)
	Student	525 (20.56)	468 (39.46)	57 (4.18)
	Employee of the private or state sector	590 (23.10)	111 (9.33)	479 (35.12)
History of high-risk behaviors	Yes	1787 (66.56)	822 (65.29)	961 (67.63)
	No	898 (33.44)	437 (34.71)	460 (32.37)
History of HBV in family members	Yes	85 (3.31)	45 (3.66)	39 (2.93)
	No	2478 (96.69)	1186 (96.34)	1290 (97.07)
National HBV vaccination	Yes	1273 (46.80)	-	-
	No	1447 (53.20)	-	-

HBV: Hepatitis B virus

Table 2: Results of the logistic regression model for factors predicting hepatitis B virus infection acquisition (2720 participants)

Variable		Total			Vaccinated Group			Unvaccinated Group		
		P value	OR	95% CI for OR	P value	OR	95% CI for OR	P value	OR	95% CI for OR
Gender	Male	Ref.			Ref.			Ref.		
	Female	0.766	1.06	0.69-1.62	0.056	2.54	1.03-7.14	0.308	0.76	0.44-1.27
Education	Elementary or middle school	Ref.			Ref.			Ref.		
	High school	0.830	1.05	0.66-1.73	0.708	0.81	0.32-2.94	0.425	1.25	0.73-2.28
	Diploma	0.789	0.93	0.58-1.52	0.237	0.59	0.21-1.33	0.236	1.49	0.79-3.06
	Academic/ university	0.761	0.92	0.54-1.47	0.831	0.92	0.43-1.86	0.632	0.83	0.35-1.66
Occupation	Self-employed	Ref.			Ref.			Ref.		
	Homemaker	0.035	1.80	1.04-3.13	0.339	1.69	0.61-5.37	0.068	1.93	0.95-3.94
	Student	0.054	1.78	0.98-3.21	0.186	2.04	0.75-6.41	0.229	1.75	0.65-4.16
	Employee of the private or state sector	0.053	1.58	0.99-2.52	0.067	2.96	0.93-9.96	0.379	1.25	0.75-2.09
History of any high-risk behavior	No	Ref.			Ref.			Ref.		
	Yes	0.022	1.48	1.06-2.10	0.085	1.60	0.95-2.80	0.089	1.46	0.95-2.31
Family history of HBV infection	No	Ref.			Ref.			Ref.		
	Yes	<0.001	2.53	1.47-4.19	0.361	1.51	0.56-3.43	<0.001	3.33	1.79-5.94
National HBV vaccination	No	Ref.			-	-	-	-	-	-
	Yes	0.004	0.57	0.39-0.83	-	-	-	-	-	-

HBV: Hepatitis B virus

infection in their family members were about 2.5 times more likely to have HBV infection. In terms of occupation, the chance of infection was lower among self-employed individuals, although this decrease was only significant when compared with homemakers. Individuals with high-risk behaviors also had a 48% higher chance of HBV infection. Variables such as gender and education had no significant association with HBV infection (table 2).

The analysis based on vaccination status showed that a family history of HBV infection significantly increased the odds of infection by more than threefold in the unvaccinated group (P< 0.001, OR=3.33), while there was no such significant association in the vaccinated group (P=0.361, OR=1.51). Stated differently, the effect of family history as a risk factor for HBV infection was diminished by national HBV vaccination (table 2).

Important Classifiers for HBV Infection

According to the results of the conditional tree method, a family history of HBV infection (P<0.001) and vaccination status (P=0.023) were two important factors in classifying individuals for HBV infection (figure 1). In the cases without a family history of infection, the risk of HBV infection was 7%, whereas, in individuals with a family history of HBV infection, the risk was related to the vaccination status of the subjects: 9% in the vaccinated group and 32% in the unvaccinated group. Thus, the effect of family history as a risk factor for HBV infection was weakened by national HBV vaccination.

Importance of Variables

The conditional forest showed that the most important variables in predicting the status of HBV infection were vaccination status and a family history of HBV infection insofar as 67% of all infection cases were predicted by these two variables. Based on the random forest, occupation and vaccination status were the most important variables in that they predicted 63% of the cases of HBV infection (figure 2).

Comparisons of the Methods

Receiver operating characteristic (ROC) curves were drawn upon to examine the efficacy of the logistic regression and various machine learning methods in predicting HBV infection in the participants (figure 3). ROC curves are used to judge the discrimination ability of different statistical methods or various tests, and the area under the curve (AUC) is an index to measure the performance of a test or method, with a higher AUC indicating a more optimal performance of the test.[34] The highest values of the AUC belonged to the random forest (AUC=74.6%), the conditional forest (AUC=71.4%), the logistic regression (AUC=60.3%), and the conditional tree (AUC=53.6%), respectively. In other words, the random forest provided the best predictions.

The comparisons of the methods using accuracy and Brier score indices is indicated in table 3. The findings indicated no considerable difference between the models, but the logistic regression model appeared to have somewhat a higher accuracy and a lower Brier score.

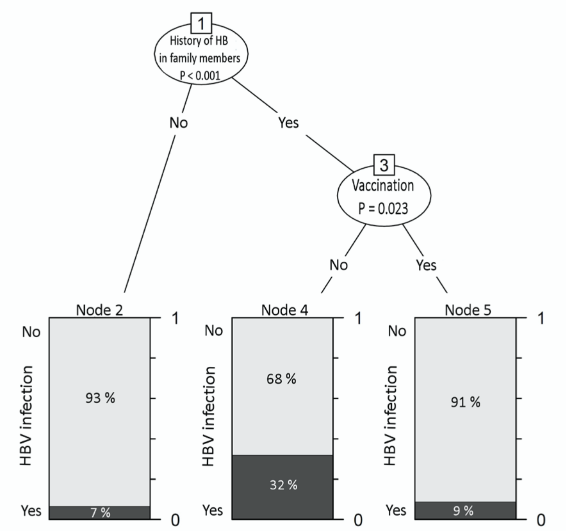

Figure 1: This figure shows classifying of persons acquiring HBV infection based on the prognostic factors by conditional inference tree. HBV: Hepatitis B virus

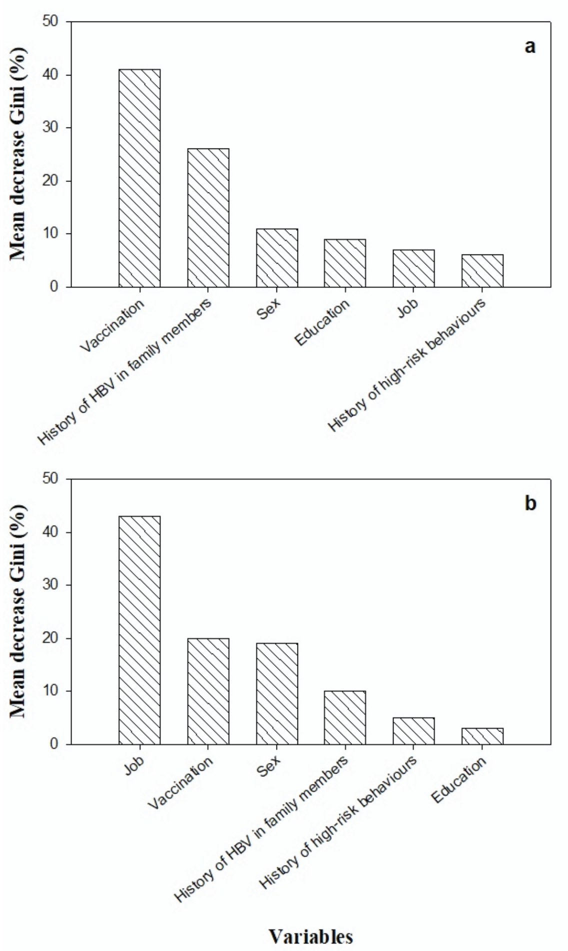

Figure 2: These figures show the normalized importance of the factors for predicting hepatitis B virus (HBV) infection acquisition, respectively, according to the conditional (a), random, (b) and forest methods.

Discussion

In the present study, the results of multivariate logistic regressions showed that HBV infection was affected by such factors as a family history of HBV infection, national HBV vaccination, high-risk behaviors, and occupation. Other variables, including gender and education, were not significantly associated with HBV infection.

The results of a study assessing the risk

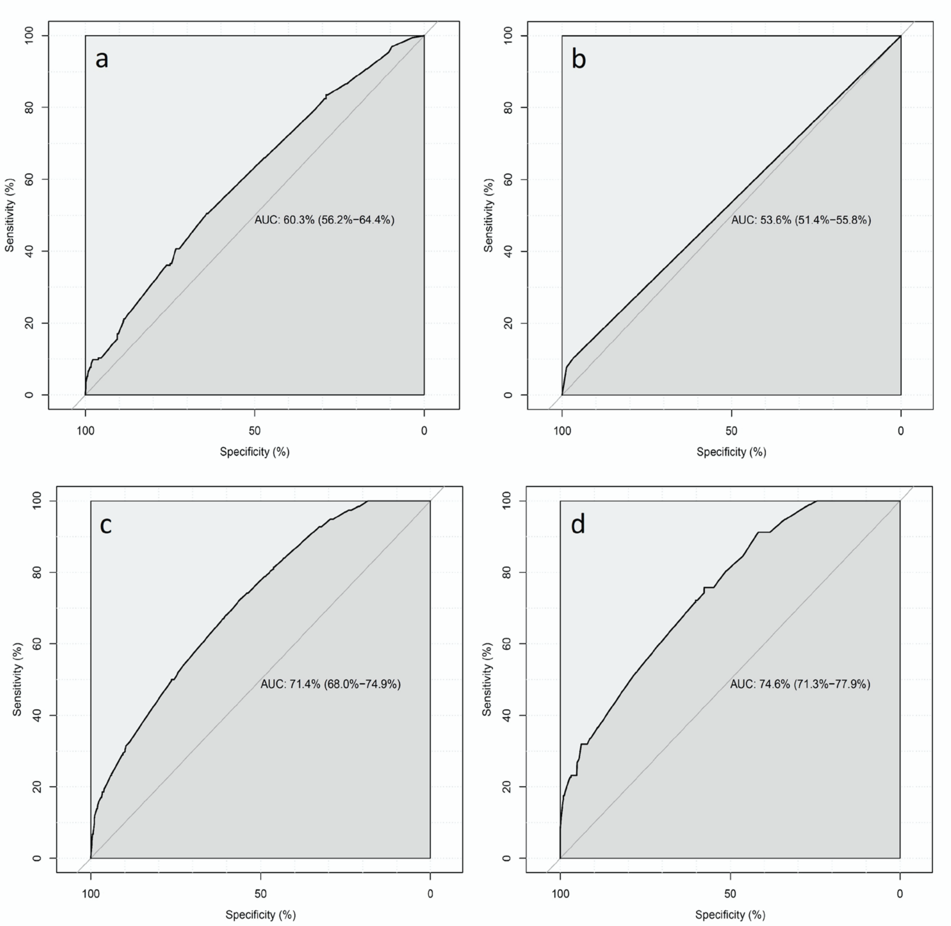

Figure 3: These figures show receiver operating characteristic (ROC) curves in the prediction of hepatitis B virus (HBV) infection acquisition based on the prognostic factors, respectively, according to the logistic regression (a), conditional tree (b), conditional forest (c), and random forest (d) methods.

Table 3: Results of assessing the goodness of fit for the different models in predicting the prognostic factors for hepatitis B virus infection acquisition (2720 participants)

Method	Accuracy	Brier Score
Logistic regression	0.928	0.066
Conditional tree	0.928	0.067
Conditional forest	0.927	0.066
Random forest	0.926	0.068

factors for HBV infection showed that a family history of the infection was strongly associated with HBV infection, which is consistent with the findings of the present study.[35] A cross-sectional study in Nepal evaluated mothers and their children under 5 years of age for HBsAg and showed that HBsAg was positive in 56% of the children who had received three doses of HBV vaccine,[36] which does not fully chime in with the results of the present study. One reason for this inconsistency in the findings may lie in the fact that the National Hepatitis B Vaccination Program in Nepal starts at 6 weeks of age, whereas most cases of transmission occur at birth or early life (the first five days) in countries with high endemicity.[36] An investigation on the risk factors for HBV infection demonstrated no relationship between gender and HBV infection,[22] which is concordant with the results of our study. A multicenter population survey conducted in Brazil concluded that the relationship between gender and HBV infection was related to geographical regions inasmuch as the association was significant in some areas and insignificant in others. Additionally, the multivariate logistic regression model in that study revealed that high-risk behaviors such as tattoos, surgery, dental services, and blood transfusion did not have a significant association with HBV infection,[37] which is in contrast with our findings. A possible reason for this discrepancy is that the study in Brazil categorized and analyzed each of these behaviors separately, whereas we considered all of them to be one variable.

In our unvaccinated group, as opposed to our vaccinated group, a family history of HBV infection significantly increased the chance of HBV infection. A reasonable explanation for this difference could be the protective effect of the national HBV immunization program, which not only has directly decreased HBV infection but also may have lessened the effects of other risk factors such as a family history of HBV infection. According to the results of a previous study, in infants who even received the first dose of HBV vaccine after 6 months of age, the prevalence of HBsAg was significantly higher than that in those who received this dose on time.[7] A study in Colombia showed that one of the factors affecting the status of HBV carriers was a delay in receiving the first dose of HBV vaccine, even in infants who received the first dose of HBV vaccine after two months of age.[38]

Based on the conditional tree utilized in the current study, two variables that affected the classification of individuals in terms of HBV infection status were a family history of HBV infection and vaccination status. In predicting disease status, vaccination status and a family history of HBV infection were of the highest significance according to the conditional forest, while occupation and vaccination status had the most importance based on the random forest. In short, these methods showed that a family history of HBV infection, vaccination status, and occupation significantly affected the status of HBV infection. According to a study in China between 1992 and 2005, the HBsAg prevalence rate was 1.3% in children with complete vaccination, 2.9% in children with incomplete vaccination, and 5.0% in unvaccinated children, indicating the effect of vaccination.[7] In addition to the role of vertical transmission from mother to child, one of the possible reasons for the association between a family history of HBV infection and the risk of the infection can be the common social context of family members, which can lead to similar behavioral risk factors among the members of the same family. The results of a study that investigated the risk factors for HBV infection showed that a family history of HBV infection was one of the risk factors for increasing the odds of positive HBsAg.[39]

Our findings indicated that 3.3% of the study participants had a history of HBV infection in their families. This low percentage may be due to the self-reporting problem originating from the social stigma surrounding HBV infection and its transmission routes, as well as previously unidentified HBV infection or unawareness about the status of HBV infection in family members. Our results may have, therefore, been affected by these issues, which should also be taken into account in future studies.

We used various models to determine the factors associated with HBV infection. Each of these methods has some advantages. The conditional tree provides homogeneous subsets of the population based on factors related to a certain probability of HBV infection acquisition and related P values. The random forest and the conditional forest determine the importance of variables; they had the highest values of AUC for predicting HBV infection in our study participants. Our comparisons of the methods using accuracy and Brier score indices showed that there was no significant difference between the models and the identified effective factors largely overlapped between these methods, although the logistic regression model appeared to have somewhat a higher accuracy and a lower Brier score.

The World Health Organization (WHO) seeks to eliminate HBV infection by the year 2030, to reduce 90% of new chronic infections, and to lower the mortality of this infection by 60%.[13] In light of the findings of the current investigation concerning the factors associated with HBV infection, we recommend that future prospective studies on all age groups be undertaken to assist health authorities in the elimination of HBV infection. To that end, educational programs are essential to educating the general population about the factors that are associated with HBV infection to prevent the infection and its irreversible complications.

The present study is the first of its kind to investigate, 25 years since the introduction of national HBV immunization in Iran, the efficacy of this routine vaccination program in reducing HBV infection and its associated risk factors. For the purposes of the study, not only did we use the classical method of logistic regressions but also we benefited from machine learning methods to predict factors affecting HBV infection. Another salient strong point of this study is that we measured the effect of these factors in vaccinated and unvaccinated groups, separately.

One of the limitations of this study is related to vaccinated and unvaccinated individuals. The fact that the coverage of the national HBV vaccination program in Iran is close to 100% precluded the selection of unvaccinated individuals after the year of the program's implementation (1993).[23] As a result, we selected vaccinated individuals from those born in 1994 and after and unvaccinated individuals from those born in 1992 and before. However, to lower the impact of this problem and reduce the age difference between the groups, we considered the age range of the participants to be between 17 and 50 years old. Another weakness of note is that despite our efforts to minimize problems related to blood sampling by selecting our study participants from individuals undergoing the mandatory premarital screening tests, we may have increased selection bias. Hence, caution should be exercised in generalizing the results of this study. What should also be considered in the interpretation of the results is that we did not evaluate all risk factors that could be associated with HBV infection. Future investigations should, therefore, include a larger number of possible risk factors for HBV infection.

Conclusion

This is the first study in Iran to investigate the factors, especially the national HBV immunization program, affecting HBV infection. The results of the various methods employed in this study demonstrated that HBV infection was affected by such factors as a family history of HBV infection, national HBV vaccination, and occupation. Additionally, the comparisons of the vaccinated and unvaccinated groups indicated that the national HBV vaccination program not only has directly reduced HBV infection but also has potentially decreased the risk associated with other variables such as a family history of HBV infection. It appears that HBV vaccination, implemented by the Iranian Ministry of Health and Medical Education in 1993, has reduced HBV infection. However, given the age range of the participants, the generalization of the results should be done with caution. The random forest was the most efficient method for predicting HBV infection in the study participants, and the logistic regression model appeared to confer the best goodness of fit.

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Conflict of Interest: None declared.

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