ORIGINAL ARTICLE

The frequency, related cause of disease, and treatment of hepatitis B virus infection: A systematic review and meta-analysis in Iran

Gholamreza Kalvandi[1], Ghobad Abangah[2], Yousef Veisani[3], Hassan Nourmohammadi[4], Mohamad Golitaleb[5], Hamed Tavan[6*]

[1]Associate Professor of Pediatrics Gastroenterology Department of Pediatrics, School of Medicine Besat Hospital, Hamadan University of Medical Sciences, Hamadan, Iran, [2]Associate Professor of Gastroenterology and Hepatology, School of Medicine, Shahid Mostafa Khomaeini Hospital, Ilam University of Medical Sciences, Ilam, Iran, [3]Research Assistant Professor of Epidemiology Department of Epidemiology, School of Health Psychosocial Injuries Research Center Ilam University of Medical Sciences, Ilam, Iran, [4]Assistant Professor of Hematology and Oncology, Department of Internal Medicine, School of Medicine,Shahid Mostafa Khomaeini Hospital, Ilam University of Medical Sciences, Ilam, Iran, [5]Instructor of Critical Care Nursing Department of Nursing, School of Nursing Arak University of Medical Sciences, Arak, Iran, [6*]MSs of nursing Medical-Surgical, Clinical Research Development Unit, Shahid Mostafa Khomeini Hospital, Ilam University of Medical Sciences, Ilam, Iran

Background: Hepatitis B virus (HBV) is one of the most dreadful viruses causing high mortality rates and serious damages to hepatocytes. The aim of this study was to assess the frequency, related causes/risk factors, and treatments of HBV infection in Iran by systematic review and meta-analysis. **Materials and Methods:** The data were obtained by a literature search in the PubMed, Scopus, SID, and Web of Sciences databases. Keywords included prevalence, risk factors, causes, treatment, and HBV. The Persian equivalents of these keywords were also searched. The time span included 2004 to2021. The Q and I^2 statistics were used to check heterogeneity among studies. The data were analyzed using Stata (version 14). **Results:** The frequencies of HBV infection and its pharmaceutical therapy were P = 6% (95% confidence interval [CI]: 4–9, I^2 = 95.2%, P < 0.001) and 19% (95% CI: 18%–30%, I^2 = 98.9%, P < 0.001), respectively. The most common risk factors/causes of HBV were narcotic consumption, blood-related factors, and transmission from infected individuals with the respective frequencies of 27% (95% CI: 16%–38%, I^2 = 88.7%, P < 0.001), 32% (95% CI: 11%–53%, I^2 = 99.8%, P < 0.001), 25% (95% CI: 10%–41%, I^2 = 99.3%, P < 0.001), and 15% (95% CI: 7%–22%, I^2 = 98.4%, P < 0.001), respectively. **Conclusion:** The most important causes of HBV infection were transmission from infected people, narcotic consumption, and blood-related factors. The main therapeutic intervention for HBV was pharmaceutical therapy.

Key words: Hepatitis B virus, frequency, treatment, meta-analysis

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INTRODUCTION

Hepatitis B virus (HBV) is responsible for a human viral infectious disease inflicting major damages to the patient's hepatic tissue.[1,2] HBV can cause both acute and chronic infections.[3] In most infected individuals, there are no signs of the disease at initial phases.[4] In others; however, the disease may acutely present with nausea, icter, fatigue, black urine, and abdominal pain.[5] Nevertheless, the window period may last 30–180 days. In the individuals affected with HBV at birth, more than 90% of the cases progress toward a chronic disease. This is while chronic HBV is observed in <10% of the patients infected after 5 years of age.[6] The majority of patients with chronic HBV do not show any sign of the disease; nevertheless, the disease still can progress to hepatic cirrhosis and cancer (hepatocellular carcinoma).[7] This phenomenon (concomitant HBV infection and cirrhosis) increases the mortality rate (as high as 15%–25%) in these patients.[7]

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Address for correspondence: Dr. Hamed Tavan, Clinical Research Development Unit, Shahid Mostafa Khomeini Hospital, Ilam University of Medical Sciences, Ilam, Iran, E-mail: hamedtavan@gmail.com

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HBV is transmitted by being exposed to contaminated blood or other biological products. In endemic regions with a high penetrance of HBV, transmission at birth and being infected via blood products at childhood are the most common ways of the spread of the virus.[8] In regions with a low prevalence, HBV is most commonly transmitted by sharing contaminated syringes for infusing intravenous narcotics among addicts, as well as via unprotected sexual intercourse.[9]

The clinical symptoms of HBV include abdominal pain, black urine, fever, joint and muscle pain, nausea and vomiting, yellowish discoloration of skin and the white of the eye, as well as fatigue and weakness.[10] The common ways of HBV transmission include unsafe sexual intercourse, using contaminated syringes, mother-to-child transmission, and transfusion of contaminated blood products.[11] The most frequent used HBV therapeutics are nucleoside/nucleotide analogs (NAs). However, these therapeutics only halt the virus proliferation and rarely eradicate it, which limits the cure rate of HBV infection.[12] HBV vaccination is the most effective preventive measure against this infection. By triple vaccination (including 3–4 infusions on multiple occasions), it is possible to prevent as high as 95% of HBV infections.[13]

One of the advantages of meta-analysis studies is the pooling of the results of valid studies conducted on a certain issue. Therefore, the results of meta-analyses can be regarded among the most credible scientific data.[14,15] Furthermore, meta-analyses are necessary to validate the results obtained by various studies and to provide a precise and reliable scale for both researchers and policymakers. The present study aimed to assess the frequency, causes, risk factors, and therapeutic modalities of the HBV infection in Iran by systematic review and meta-analysis.

MATERIALS AND METHODS

The data were obtained by searching the studies conducted in Iran in the PubMed, Scopus, Web of Sciences, and SID databases. Keywords included hepatitis B virus, treatment, prevalence, and causes, as well as their Persian equivalents. The articles published within 2004–2021 were included.

Study selection and data extraction

Initially, all the Iranian studies related to HBV were collected. After the primary search, a checklist was prepared for recording the specifications of each study. All the articles with the phrases of "HBV treatment in Iran" and "the etiology and complications of HBV in Iran" entered into the primary checklist. The studies assessing surgical therapies, coping and preventive measures, as well as HBV risk factors were omitted at this stage.

A second checklist was prepared for obtaining required information from the primary screened studies (i.e., the first author's name, title, year of study publication, location, sample size, number of women and men, HBV total prevalence, HBV prevalence in men and women, age groups, therapeutic interventions and their subgroups, as well as a specific code for the location of the study). After scrutinizing the final checklist, the articles related to the study's aims were selected for meta-analysis.

Selection and qualification of studies

The STROBE checklist[14,15] was used to evaluate the articles. Two of the authors independently gave each part of the checklist a score between 0 and 2. Based on the scores obtained from the checklist, the qualities of the articles were designated as weak, moderate, and good with the scores of 1–15, 16–30, and 31–44, respectively. The articles that received at least 16 scores were included in the meta-analysis phase.

In the primary literature search, 100 studies were obtained using the keywords. Out of these, 12 articles entered the checklist prepared for study qualification. At this stage, the studies were assessed for extracting required information (1 – sample size, 2 – year of publication, 3 – HBV treatment subgroups including medical therapeutics, and 4 – causes of the disease).

The studies evaluating HBV treatment in Iran were finally approved. Accordingly, 12 studies entered the meta-analysis phase after studying their full texts in detail [Figure 1].

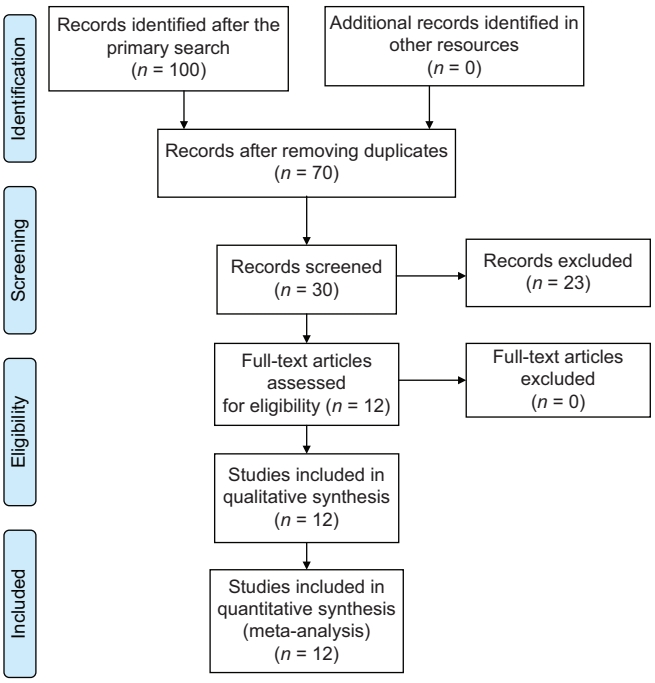

Figure 1: The flowchart for including studies in meta-analysis

Statistical analysis

The variance of each study was calculated using normal and bi-nominal distributions. Weighted mean was applied for synthesizing the HBV prevalence reported in different studies. Each study was assigned with a weight inversely correlated with its variance. Considering the wide spectrum of HBV prevalence reported in different studies (i.e., heterogeneous studies) and a statistically significant heterogeneity index (I^2), the random-effects model was used for meta-analysis. The heterogeneity rate was 92.1%, rendering a high heterogeneity. The I^2 index is a numerical value for estimating the variance ratio between studies and is utilized as a surrogate for the probability index. The I^2 values of ≤25%, 26%–50%, 51%–75%, and 76%–100% indicate low, moderate, significant, and high heterogeneity, respectively.[16-17]

Meta-regression was utilized to determine hepatitis B treatment in separate years and to evaluate the reasons of heterogeneity among the studies. The cure rate of HBV in Iran was calculated based on different risk factors and age groups by subgroup analysis. The data were analyzed by Stata (version 14) software.

RESULTS

The finally included studies had been published from 2004 to 2021. The total sample size was 10815 (i.e., 901 subjects per study). The data extracted from the qualified studies included hepatic functional tests, the causes of the HBV infection, and HBV treatments.

The highest and lowest HBV frequencies were reported by Azad *et al.* (11.25%) in Qom in 2020[29] and Navaifar *et al.* (1.57%) in Sari in 2020,[28] respectively. The features of the studies reporting HBV treatments are shown in Table 1. HBV risk factors, hepatic functional tests (aspartate transaminase [AST], alanine transaminase [ALT], and alkaline phosphatase [ALP]), and HBV treatments are demonstrated in Table 2. Other parameters related to the HBV infection are also presented in Table 3.

The forest plot of HBV frequency is presented for each study in Figure 2, and Figure 3a shows the meta-regression of the HBV infection in separate years.

Table 1: The main characteristics of the included studies

First author	Location	Year	Total (*n*)	Female (*n*)	Male (*n*)	Hepatitis B (%)
Teymoorzadeh *et al.*[18]	Tehran	2014	230	100	130	10.46
Pourshams *et al.*[19]	Tehran	2004	1035	597	438	4.25
Ebrahim Zadeh *et al.*[20]	Birjand	2015	301	138	163	-
Bakhshizadeh *et al.*[21]	Tehran	2015	93	21	72	8
Mohammadzadeh *et al.*[22]	Tehran	2017	300	86	214	10
Mokhtarifar *et al.*[23]	Mashhad	2014	749	245	504	-
Alavian *et al.*[24]	Tehran	2005	280	73	207	7.7
Somi *et al.*[25]	East Azerbaijan	2020	3172	1602	1571	
Mokhtari *et al.*[26]	Shiraz	2021	2814	1541	1273	7.1
Gholamzadeh Khoei *et al.*[27]	Qazvin	2020	488	407	81	3.3
Navaifar *et al.*[28]	Sari	2021	1018	1018	0	1.57
Azad *et al.*[29]	Qom	2020	1600	-	-	11.25

Table 2: Treatments, risk factors, and liver functional tests for the hepatitis B infection reported in the included studies

Article (first author)	Treatment (%)	Risk factors (%)				Liver functional tests (%)		
		Cigarette smoking	Underlying illnesses	Blood-related factors	Contact with an infected person	ALK	ALT	AST
Teymoorzadeh *et al.*[18]	9.5	32.5	23.5	-	-	-	-	-
Pourshams *et al.*[19]	-	-	34.1	9.1	72.7	-	-	-
Ebrahim Zadeh *et al.*[20]	14.3	-	30.2	9.3	22.2	10.36	77	57
Bakhshizadeh *et al.*[21]	18.8	-	-	-	-	-	-	-
Mohammadzadeh *et al.*[22]	14.48	21.3	26.8	30.3	42.4	-	-	-
Mokhtarifar *et al.*[23]	-	-	13.5	30.3	37.2	-	-	-
Alavian *et al.*[24]	-	-	35.6	25	28.4	-	79.73	37
Somi *et al.*[25]	-	-	-	-	-	-	-	-
Mokhtari *et al.*[26]	24.7	-	-	-	-	-	-	-
Gholamzadeh Khoei *et al.*[27]	-	-	-	-	-	-	-	-
Navaifar *et al.*[28]	46.6	-	-	-	-	-	-	-
Azad *et al.*[29]	-	-	-	-	-	-	-	-

ALT=Alanine transaminase; AST=Aspartate transaminase; ALK=Alkaline phosphatase

Table 3: The pooled prevalence of the treatments and causes of the hepatitis B infection

Variables	Subgroups	Articles, *n* (%)	95% CI	I^2	*P*
Hepatitis B (%)	Total	10 (6)	4-9	95.2	0.000
Medical treatment	Total	7 (19)	18-30	98.9	0.000
Cause/risk factors of the disease	Tobacco use	2 (27)	16-38	88.7	0.003
	Underlying illnesses	6 (25)	10-41	99.3	0.000
	Blood-related factors*	5 (15)	7-22	98.4	0.000
	Contact with an infected person**	6 (32)	11-53	99.8	0.000

*Blood-related factors=Tattoos, blood transfusion, dental instruments; **Contact with an infected person causing the transmission of the disease=Sexual contact, the umbilical cord blood. CI=Confidence interval

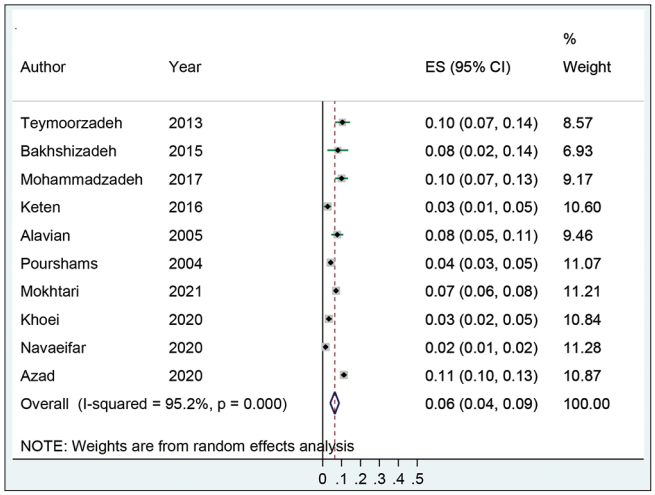

Figure 2: The forest plot of hepatitis B virus prevalence with 95% confidence interval. The frequency of hepatitis B virus in individual studies. The overall prevalence of hepatitis B virus was *P* = 6% (95% confidence interval: 4–9, I^2 = 95.2%, *P* < 0.001). The lines represent the confidence intervals of hepatitis B virus prevalence in each study. The middle point on each line shows the estimated hepatitis B virus prevalence in each study, and the diamond-shaped figure demonstrates the overall confidence interval of hepatitis B virus prevalence

Figure 3b shows HBV meta-regression based on the sample size, revealing a lower HBV prevalence in the studies with larger sample sizes. Publication bias is presented in Figure 4.

As shown in Figure 4, the symmetrical appearance of the funnel plot indicated no publication bias in the assessed studies. The circles "sizes exhibit the studies" weights (i.e., bigger circles reflect larger sample sizes).

DISCUSSION

HBV is responsible for one of the most dreadful viral hepatic infections. Hepatitis (i.e., liver inflammation) is caused by a variety of viruses that induce hepatic inflammation and liver injury.[6-8] In the present study, we assessed HBV prevalence in various geographical regions of Iran. The overall prevalence of HBV was obtained as 0.7%. In a review study in Iran, the overall prevalence of chronic HBV infection was reported to be 1.7%. Furthermore, chronic HBV infection has been reported in 3.2% and 1.5% of intravenous drug users and β-thalassemia major patients, respectively.[30]

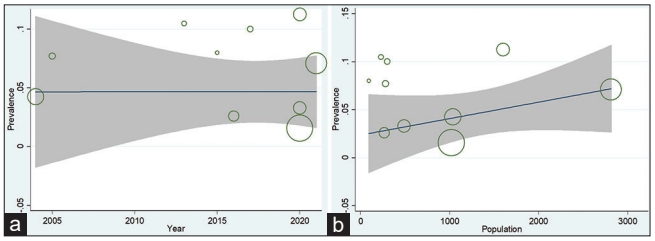

Figure 3: (a) The meta-regression of hepatitis B prevalence in separate years. Hepatitis B prevalence meta-regression in each year. The annual prevalence of hepatitis B virus has increased since 2005 toward 2021. (b) The meta-regression of studies based on the sample size. The meta-regression of hepatitis B prevalence based on the sample size. The prevalence of hepatitis B virus was lower in the studies with larger sample sizes

This shows an overall combined prevalence of 6% in these groups, which is in line with the results of the present study.

According to our results, and based on the data obtained in various studies conducted in different regions of Iran, the overall rate of pharmaceutical treatment for HBV-infected patients was obtained 12%. Antiviral therapies are considered the most effective treatments for HBV infection.[20-22] In the present study, liver functional tests showed the mean levels of 47, 78, and 10.36 IU/L for AST, ALT, and ALP liver enzymes, respectively. As the HBV infection is a blood-borne disease affecting hepatocytes, an elevation in the liver enzymes can be the primary sign of severe liver damage.[13-15]

Educating vulnerable and at-risk people can reduce the incidence of HBV infection. In addition, since HBV infection is a blood-borne disease, it is advisable for vulnerable people, including hospital staff and those who are in direct contact with the blood, to be vaccinated against the virus to upgrade their safety levels.[31,32]

According to our findings, the main risk factors of HBV infection included the use of narcotics, suffering from underlying diseases, blood-related factors, and disease transmission from an infected person with the frequencies of 41%, 30%, 27%, and 18%, respectively. In addition, other studies have mentioned that lifestyle can be an important risk factor for the disease. Blood-related risk factors are the most important ways of HBV transmission among the addicts sharing syringes for injecting intravenous drugs, as well as

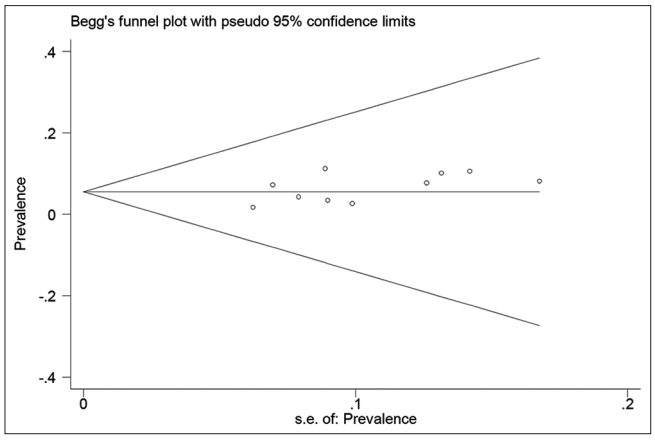

Figure 4: The publication bias regarding hepatitis B prevalence and its pharmaceutical therapies

among health-care providers who are in direct contact with the blood and blood products.[31,32] Overall, it is presumable that environmental and occupational parameters are critical players that increase the risk of HBV infection. Therefore, these factors should be controlled to effectively confine the spread of the disease. This is a prerequisite for treating and supporting HBV-infected patients.

HBV meta-regression based on the year of study conduction showed a rise in HBV prevalence from 2005 to 2021. This observation demonstrated the inability of scientific achievements to effectively manage the disease, which may be partly due to the higher rates of unprotected sexual contacts, donation of infected blood products, and seeking health care from unapproved facilities (such as dentistry or tattoo centers).[32,33] This shows that the disease has not yet been taken seriously by the community. Therefore, boosting awareness about the disease may significantly reduce its prevalence and help save its costs and reduce its complications and hospitalization rate.

Limitations

A limited number of disease-related variables had been mentioned in some of the assessed studies. Some of the studies reported etiologies, risk factors, symptoms, and treatments in separate categories, with no overall estimations. Furthermore, there were no comparisons between different age groups in some of the studies, and the following-up duration had not been reported in some others. Finally, some studies did not describe therapeutic interventions other than pharmaceutical therapies, curbing to determine the best therapeutic strategy in these patients.

Recommendations

Based on our findings, contact with infected individuals, suffering from underlying comorbidities, using narcotics, and finally, blood-related factors constituted the most prominent HBV risk factors. It is important to implement screening tests to identify at-risk individuals and therefore manage the disease spread. Timely diagnosis of underlying conditions (i.e., cancer) may be effective to prevent liver cirrhosis. It is also amenable to boost social knowledge about narcotics and their associated diseases by producing educational contents and movies. This can decrease the incidence of HBV infection. It is advisable for people to seek health-care services from safe facilities to prevent HBV transmission via infected blood products.

CONCLUSION

The major risk factors of HBV infection were disease transmission via infected individuals, suffering from underlying conditions, using narcotics, and blood-related factors. Pharmaceutical treatments included the most important therapeutic strategy in HBV-infected patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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