

Hepatitis B Virus Infection in Iranian Hemodialysis Patients A Systematic Review and Meta-Analysis

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Introduction. Hepatitis B virus (HBV) infection in hemodialysis patients and its associated adverse health consequences are a worldwide health priority. This systematic review aimed to provide evidence on HBV infection in Iranian hemodialysis patients.

Materials and Methods. Through a comprehensive systematic review of literature, which led to meta-analysis of findings, we estimated the pooled prevalence of HBV infection in Iranian hemodialysis patients. The main international electronic data sources were MEDLINE, Institute of Scientific Information, and Scopus. We also search several Persian-language databases. All cross-sectional and analytical studies conducted in Iran concerning HBV infection were included irrespective of date and language. **Results.** Of 602 publications retrieved from literature search, 66 met the inclusion criteria, and 36 were eligible for including in the study. The prevalence rate varied from zero to 9.75% across different provinces. The national prevalence of HBV was reported between 2.1% and 18.2%. Significant heterogeneity was found between reported prevalence rates ($I^2 = 83.5\%$, P < .001), as a result of which, we used random effect analysis. Results of metaanalysis showed that the estimated pooled prevalence was 4% (95% confidence interval, 3.3% to 4.7%).

Conclusions. To our knowledge, this was the first comprehensive systematic review of HBV infection in the hemodialysis patients of Iran. Results could be useful for informed health policy making and planning further studies in this field.

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INTRODUCTIONS

Hemodialysis is a life-saving procedure in patients with end-stage renal disease that could be considered for eligible ones for whom all other therapeutic choices have failed. Of all important complications, blood-borne diseases are serious side effects of hemodialysis. Studies have shown that the prevalence of various types of hepatitis viruses among hemodialysis patients is higher than the general population and patients undergoing long-term hemodialysis potentially have an increased risk of exposure to infections with hepatitis B virus (HBV) and other blood-borne diseases. ^{3,4} It

is estimated that worldwide more than 240 million people are chronic HBV carriers, and every year, more than 780 000 deaths occur due to complications of HBV infection.^{5,6}

Evidence shows that the prevalence of end-stage renal disease is increasing in Iran.² On the other hand, a systematic review done in 2008 showed that despite 94% coverage of vaccination program against HBV in 2005, about 2.5% (95% confidence interval, 1.2% to 9.7%) of Iranians were infected with HBV between 2001 and 2007.⁷ Another study remarked that 2.2% of Iranian general population were infected with HBV; therefore, Iran is among countries with a low-intermediate HBV prevalence rate.⁸

According to a recent review study in Iran, the prevalence of occult HBV infection hemodialysis patients is 3.11%, which is lower than those in Italy (26.6%), Egypt (4.13%), and Turkey (16.9%), the seems that those in the United States (3.8%). It seems that variation of prevalence of HBV in hemodialysis patients does not follow any specific geographic patterns. Another important point is a positive association between the duration of dialysis and positivity of HBV in the hemodialysis patients in Iran. Italians is a positive association between the duration of dialysis and positivity of HBV in the hemodialysis patients in Iran.

Hepatitis B virus infection in hemodialysis patients is a risk factor for impaired parathyroid hormone, hepatocellular carcinoma, and cirrhosis; therefore, it is critical to generate information for planning better strategies of prevention and control. Despite the priority of the problem, there is not enough data to support policies and programs. On the other hand, studies have shown different prevalence rates across different provinces, and none are focused on specific high-risk populations such as hemodialysis patients. The current study was designed to investigate the prevalence of HBV and probable related factors to heterogeneity of prevalence Iranian hemodialysis patients.

MATERIALS AND METHODS Study Design and Inclusion Criteria

This systematic review was a comprehensive review of literature that led to meta-analysis of findings to estimate the pooled prevalence of HBV infection in Iranian hemodialysis patients. We included all cross-sectional and analytical studies conducted in Iran concerning HBV infection in hemodialysis patients. There was no limitation on age of patients, time of study conduction, time of publication, and the language of the articles.

Participants in the Studies

All participants of the included studies were hemodialysis patients from Iran with no restriction in terms of age, sex, employment, or underlying disease for which hemodialysis was needed.

Outcome

The outcome of the study was the prevalence of HBV infection among hemodialysis patients that was confirmed based on blood samples of patients with a positive hepatitis B surface antigen.

Search Strategy

To assess papers on prevalence of HBV infection in Iranian hemodialysis patients, the relevant literature was searched concentrating on specific key words of "HBV infection," "hepatitis B," "dialysis," "hemodialysis patients," and "renal transplantation," in "adult" hemodialysis patients, living in "Iran." We searched electronic databases, including main domestic databases, Iran-Medex, Scientific Information Database, and Iran-Doc, and also international databases including PubMed and the National Library of Medicine Gateway (for MEDLINE), Institute of Scientific Information, and Scopus. To obtain the most comprehensive results, we searched these data sources using Medical Subject Heading terms, EMtree, and related equal Persian keywords for Iranian databases.

We also searched related gray literature; 115 national, regional, and international medical sciences conferences were found in the study time period. Forty-seven of 115 relevant abstract books were selected and hand searched by 2 independent reviewers. We also searched the research projects of 41 of 53 Iranian universities of medical sciences from their websites. Moreover, we contacted 5 experts in HBV researchers in Iran and searched their projects for additional citations. The references and citations of relevant articles were also assessed. There was no limit for age, date, and language.

Quality Assessment and Data Extraction

Quality of selected papers was assessed using a quality assessment form which contained 3 parts as follows: general information, sampling quality, and measurement quality. Aimed to evaluate the quality of studies, we used the CASP checklists. The data was extracted from the included studies using a checklist which included citation, study year, place of study, level of study, type of study, total sample size, mean age, type of measurement, results of measurement, and other information. Search and data extraction was performed by 2 experts independently, and all data was assessed based on this checklist.

Statistical Analysis

The results were presented as prevalence and 95% confidence interval. Heterogeneity of reported prevalence between studies was assessed by the chisquare-based Q test and the *I* square statistics. The result of the Q test was regarded to be significant when *P* value was less than .10. Due to severe heterogeneity among studies regarding reported values, pooled prevalence was estimated using a random-effect meta-analysis model (using the Der-Simonian and Laird method). We undertook a meta-regression analysis of those studies with appropriate data. Forest plot was used to present results of the meta-analysis schematically. The analyses were conducted using the Stata (version 11.0, StataCorp LP, College Station, TX, USA).

Ethical Considerations

The study protocol was approved by the ethics committee of Alborz University of Medical Sciences. All of the included studies in our review would be cited in all reports and all publications of our study. Whenever we needed more information about a certain study, for obtaining required information, we contacted the corresponding author.

RESULTS

We refined data for prevalence of HBV infection in Iranian hemodialysis patients. Based on our search strategy through comprehensive searching, 602 publications were found, from which 382 papers were found from international databases, and others were from Iranian data banks. After reading the titles and abstracts, 536 of these publications were excluded because they were duplicates or were not related to objective of this study. The remaining 66 publications were retrieved for further assessments, of which 36 were eligible for including in the study (Figure 1).

Regarding the geographic distribution, we

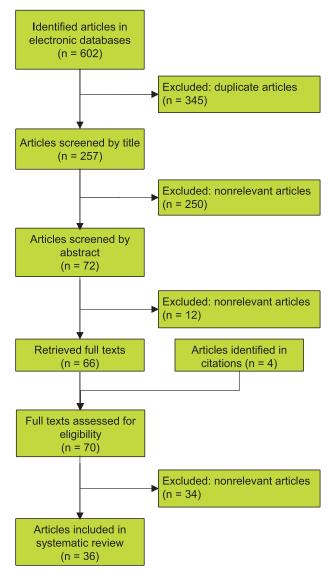


Figure 1. Article search and review flowchart for selection of studies.

found 6 national and 28 province-level reports. There were also 2 studies at the district levels. All of searched articles were in English or Persian language. Retrieving articles were assigned to studies conducted between 1975 and 2015. It is noticeable that 9 studies did not mention the study years. Maximum of mean age of patients was 62.16 ± 14.86 years and its minimum was 37.3 ± 12.11 years old. Laboratory results of 27 studies were reported based on the enzyme-linked immunosorbent assay technique (Table).

The prevalence rate of HBV infection varied from zero to 9.75% through different provinces. The national prevalence of HBV was reported between 2.1% and 18.2%. The results of heterogeneity

Included Studies on Hepatitis B Virus Infection in the Hemodialysis Patients of Iran*

First Author (Year)	Study Year	Level	Place of Study	Number of Patients	Mean Age, y	Test	Prevalence HBV (95% Confidence Interval), %
Arababadi (2009) ¹⁴	ND	Provincial	Kerman	90	60	ELISA	0 (0 to 6)
Rostami (2013) ¹⁵	2006	National	Iran	4101	ND	ELISA	2.60 (2 to 3)
Rostami (2013) ¹⁵	2011	National	Iran	4101	ND	ELISA	2.10 (2 to 3)
Mahdavimazdeh,(2009) ¹⁶	2005	Provincial	Tehran	2630	53.4	ELISA	2.40 (2 to 3)
Joukar (2011) ¹⁷	2009	Provincial	Guilan	514	54.8	ELISA	1.40 (1 to 3)
Joukar (2012) ¹⁸	2009	Provincial	Guilan	507	53.2	ELISA	1.40 (1 to 3)
Hamissi (2011) ¹⁹	2009	Provincial	Qazvin	195	53.62	ELISA	3.10 (1 to 7)
Etemadi (2012) ²⁰	ND	Provincial	Tabriz	412	54.9	ND	3.20 (2 to 5)
Keyvani (2013) ²¹	1975	National	Iran	103	60.5	ELISA	18.2 (11 to 26)
Masood (2014) ²²	2010	Provincial	Birjand	41	54.93	ELISA	9.75 (2 to 20)
Mansour (2009) ²³	2007	Provincial	Rasht	163	ND	ELISA	3.06 (1 to 6)
Assareh (2009) ²⁴	2005 -2006	Provincial	Khuzestan	214	37.3	ELISA	5.10 (2 to 8)
Alavian (2003) ²⁵	ND	Provincial	Tehran	838	50.41	ELISA	4.30 (3 to 6)
Rafiei (2011) ²⁶	ND	Provincial	Mazandaran	31	39.55	ND	0 (0 to 17)
Somi (2014) ²⁷	2012	Provincial	Tabriz	455	50.35	ELISA	3.07 (2 to 5)
Mostaghni (2011) ²⁸	2004- 2005	Provincial	Bushehr	119	48	ELISA	6.72 (3 to 13)
Khamene (2007) ²⁹	ND	Provincial	Tehran	141	45	ELISA	39.71 (32 to 48)
Khameneh (2008) ³⁰	ND	Provincial	Urmia	167	ND	ELISA	6.5 (3 to 11)
Seyrafian (2006) ³¹	2005	Provincial	Isfahan	556	ND	ELISA	2.90 (2 to 5)
Kheradpezhouh (2007) ³²	2005	Provincial	Tabriz	324	ND	PCR	4.60 (3 to 8)
Zahedi (2012)33	2010	Provincial	Kerman	228	51	ELISA	7.0 (4 to 11)
Alavian (2008) ²	2000	National	Iran	1000	49.5	ELISA	3.80 (3 to 5)
Alavian (2008) ²	2006	National	Iran	1000	54.5	ELISA	2.60 (2 to 4)
Eslamifar (2007) ³⁴	2006	National	Iran	77	52.1	ELISA	6.49 (2 to 15)
Bahri (2016) ³⁵	2015	Provincial	Bandar Abbas	153	54.06	ELISA	5.88 (3 to 11)
Shahhosseini (2001) ³⁶	ND	Provincial	Tehran	136	ND	PCR	8.09 (4 to 14)
Ramezani (2010)37	ND	Provincial	Tehran	289	55	ELISA	2.80 (1 to 5)
Hajibagheri (2000) ³⁸	ND	Provincial	Kordestan	124	ND	ELIZA	2.60 (1 to 7)
Abbasi (2012) ³⁹	2009-2010	Provincial	Golestan	100	54.6	PCR	0 (0 to 5)
Haghazali (2011) ⁴⁰	2007	Provincial	Qazvin	134	ND	ELIZA	3.70 (1 to 8)
Aminzadeh (2000) ⁴¹	1999	Provincial	Tehran	56	ND	ND	40 (26 to 53)
Khoshbaten (2003) ⁴²	2004	Provincial	Tabriz	324	53.5	ND	4.60 (3 to 8)
Aghasadeghi (2013) ⁴³	2011	Provincial	Tehran	120	55	ELIZA	7.50 (3 to 14)
Roushan (2015) ¹³	2012-2014	Provincial	Mazandaran	482	54.96	PCR	2.10 (1 to 4)
Dadmanesh (2015) ⁴⁴	2012-2013	Provincial	Tehran	138	62.16	PCR	0 (0 to 4)
Ramezani (2010) ⁴⁵	2010	Provincial	Tehran	289	55	ELIZA	6.20 (4 to 10)

^{*}HBV indicates hepatitis B virus; ND, not determined; ELISA, enzyme-linked-immunosorbent assay; PCR, polymerase chain reaction; and RIBA, recombinant immunoblot assay.

assessment demonstrated severe heterogeneity between reported prevalence rates (I^2 = 83.5%, chisquare = 212, P < .001). Due to severe heterogeneity, we used random effects analysis and results of meta-analysis showed that the estimated pooled prevalence was 4% (95% confidence interval, 3.3% to 4.7%; Figure 2). Subgroup analysis according to type of kits showed that the estimated pooled prevalence was 4% and 3% based on the enzymelinked immunosorbent assay and polymerase chain reaction techniques, respectively (Figure 3).

Results of meta regression showed that none of the variables (kit, location of study, study year, and mean age of patients) were associated with the prevalence of HBV infection (P > .05).

DISCUSSION

Patient diagnosed with end-stage renal disease need dialysis via blood or peritoneal ways; however, hemodialysis especially poses them to meet blood-borne infections like HBV and hepatitis C virus (HCV). In other words, these patients are susceptible to infections due to uremia resulting in immune deficient status.^{6,13} The prevalence of HBV among hemodialysis patients highlights the potential risk for such infection transmission.¹²

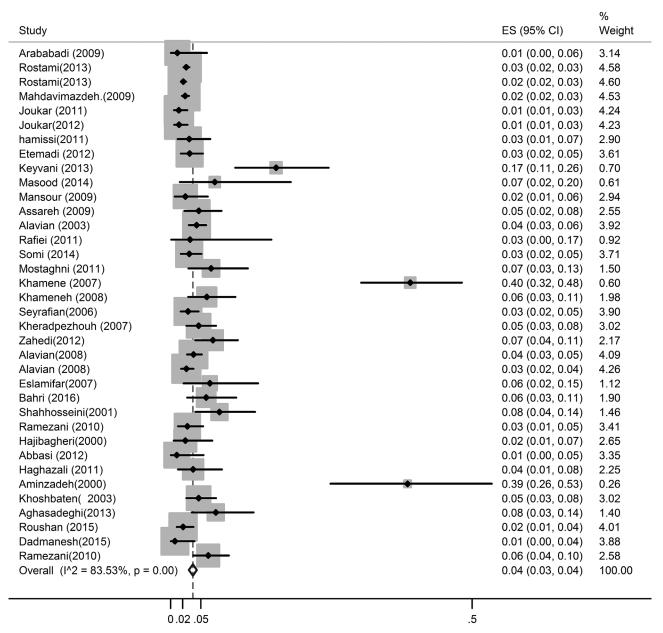


Figure 2. Prevalence of hepatitis B virus infection in Iranian hemodialysis patients.

Although the transmission way of HBV and HCV are similar, studies on co-infection of both these infections in hemodialysis patients are rare, the results show that prevalence of this co-infection is higher in patients who undergo hemodialysis; Several studies reported co-infection rates 1.2% to of 30.4%. Alashek and colleagues reported an anti-HCV-positive rate of 31.1%, hepatitis B surface antigen-positive rate of 2.6%, and a positive rate of both of 1.2%, and Dubey and coworkers reported a prevalence rate for HBV of 3% and for HCV of 0.8% in a study on hemodialysis patients. This

systematic review on national and subnational Iranian populations showed a wide range of zero to 9.75% for HBV prevalence rates at the province level and between 2.10% and 18.2% at the national level.

Despite the difficulty in single-point prevalence estimation, a previous systematic review done on HBV infection in general Iranian population verifies these results. ⁴⁹ These wide ranges would be explained by a few reasons; the first and most important one is about the national program of vaccination against HBV, which has been launched

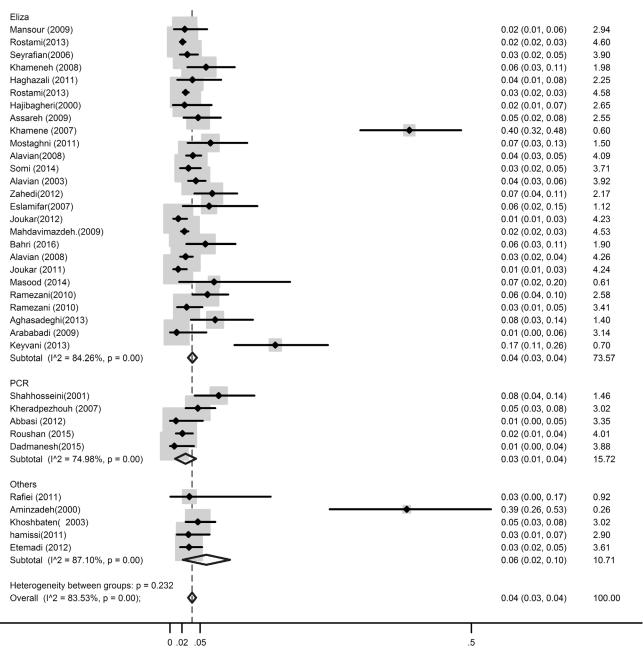


Figure 3. Prevalence of hepatitis B virus infection in Iranian hemodialysis patients according to type of kits.

since 1993, with a coverage from 62% in 1993 to 94% in 2005, which caused a significant decrease in infection rate; however, it seems that the average age of infected patients increased according to vaccination age for HBV.⁵⁰ Also, HCV infection acts like a silent epidemic in younger age groups; Fattahi and coworkers showed that a higher prevalence of HCV positivity was seen in ages of 12 years old and less.⁵¹ The second reason is related to unclear and possibly variable risks

for blood-borne diseases in particular studied populations such as intravenous drug users, prisoners, and individuals with a positive history of unsafe transfusions and transplantations, and similar ones are placed in population at high risk for blood-borne transmission.⁵²

On the other hand, duration and frequency of hemodialysis, as well as history of blood transfusion were considered as the most important risk factors of transmitted infections.^{51,53} This point is very

critical that the carrier status for individuals infected by HBV with no specific symptoms or signs is detected only through specific laboratory tests. It means that infection could be transmitted during parenteral routes like maintenance dialysis that may lead to a higher prevalence of HBV.⁵⁴ Focusing on important factors of infections such as prevalence of infection in specific populations and also human- and environmental-related factors reveal a practical framework of situation analysis that could be used in prevention and controlling management programs.⁵⁵

Most of instruments used during hemodialysis are nondisposable and serve for both seropositive and also seronegative patients. Even health workers' hands are introduced as a way of nosocomial patient-to-patient transmission in dialysis unit.⁵⁶ Also, many patients start the hemodialysis with an unclear history of vaccination and blood seromarkers which result in vulnerably to bloodborne infections for themselves and other patients. Khoso and colleagues showed that 81.6% of blood donors were never vaccinated for hepatitis B.57 Studies show that appropriate preventive procedures can control and reduce the risk of HCV infections.^{2,58} Another study from 2008 to 2013 in Iran demonstrated that due to safety measures like the national vaccination program and increasing safety of donor recruiting, the rates of transfusiontransmitted infections declined from 423 to 153 per 100 000 donors for HBV.⁵⁹ Another systematic review done in 2008 in Iran confirmed that the prevalence rates of HBV were decreasing; however, hard interventions are necessary to control these transmissible infections in high-risk patients.²

Compared with the previous studies, the present study benefited from several achievements. This study presents scientific evidence on prevalence infection of HBV among the Iranian hemodialysis patients. All available sources of data and domestic databases were searched using English and Persian search terms. As the main limitation, the validity and applicability of our systematic review depended on the quality of the primary studies that were included. As another point, heterogeneity of the searched results limited the generalization of our findings.

CONCLUSIONS

To our knowledge, this is the first comprehensive

systematic review of HBV infection in the hemodialysis patients of Iran. Results could be useful for better health policy making and more planned studies in this field. These also can be used for future complementary analyses.

CONFLICT OF INTEREST

None declared.

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