

# Oncogenic Viral Infections Among Iranian Hemodialysis Patients: A Systematic Review

## Abstract

**Introduction:** Chronic hemodialysis is a lifesaving procedure for end-stage renal failure patients who may lead to the transmission of oncogenic viral infections discussed as a major cause of liver disease and a potential cause of substantial morbidity and mortality. In this regard, the hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most common infections that studied recently. This study aimed to review systematically all available documents on the prevalence of hepatitis D virus (HED), hepatitis E virus (HEV), hepatitis G virus (HGV), human T-lymphotropic virus (HTLV), human immunodeficiency virus (HIV), and Kaposi's sarcoma-associated herpes virus (KSHV) in Iranian hemodialysis patients. **Methods:** We conducted a comprehensive systematic review of literature on the prevalence and factors associated with HED, HEV, HGV, HTLV, HIV, and KSHV in Iranian hemodialysis patients. Using Medical Subject Headings (MeSH) terms, Emtree, and related equal Persian key words, irrespective of age, date, and language, the main domestic databanks of Barekat, Scientific Information Database (SID), Iran-doc, and also international databases of PubMed and NLM Gateway (for MEDLINE), Institute of Scientific Information (ISI), and SCOPUS searched. Interest outcome of infection prevalence was confirmed based on reported positive tests of blood samples. Since the studied factors are very numerous and there is even a high heterogeneity in each factor, so the meta-analysis was not performed. **Results:** Based on our search strategy through comprehensive searching, 509 studies were found. From them, 314 articles were from international data bases and others from Iranian data banks. After excluding duplicates and overlapping studies, 41 studies were included in the analysis; 11 studies were relevant to HIV, 10 studies assigned to HEV, and 7 studies belonged to HGV field. The HDV, HTLV1,2, and KSHV were the other research subject areas. The prevalence of HIV, HGV, and HTLV1,2 ranged from 0% to 1.5%, 0% to 24.19%, and 0.6% to 70.4%, respectively, in different provinces. **Conclusions:** This is the comprehensive systematic review on oncogenic viral infections prevalence in the Iranian hemodialysis patients. Present findings emphasize on requirement to evidence-based practical intervention for better prevention and control of problem. The findings could be used as a scientific evidence for developing related policies and highlighting the future plan of complementary researches.

**Keywords:** Hemodialysis, infections, Iran, oncogenic viral, systematic review

## Introduction

Chronic hemodialysis (HD) is a lifesaving procedure for end-stage renal failure patients. During hemodialysis, the blood is filtered in a dialysis machine. Although this method can be efficient to treat renal failure, but it may also lead to the transmission of some blood borne infections, such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV).<sup>[1]</sup>

Patients undergoing hemodialysis are at high risk of exposure for infections of blood, blood product, and needle-stick injuries. In these regards, HBV and HCV are the most common viral infections. On

the other hand, infections by other viruses, such as hepatitis E, D, and G, HIV, and human T-lymphotropic virus (HTLV) lead to other considerable problems.<sup>[2-4]</sup>

After cardiovascular diseases and bacterial infections, viral hepatitis is the most frequent disease to follow as the consequence of hemodialysis treatment. The prevalence of viral hepatitis in the hemodialysis patients is much higher than the prevalence of these diseases in the general population.<sup>[2,3]</sup>

Two recent published meta-analysis studies on the prevalence of HBV and HCV in the Iranian hemodialysis patients revealed that the estimated pooled prevalence of HBV

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and HCV in Iranian hemodialysis patient was %4 (95% CI = 3.3%–7.7%) and %11 (95% CI = 10%–13%), respectively.<sup>[5,6]</sup>

Based on the results of related investigations, Iran is known as an endemic country for hepatitis E virus. The seroprevalence of hepatitis E virus (HEV) in patient groups varies from 1.1% to 14.2%. The estimation in general population and hemodialysis patients is 6.3%–28.3% and 1.6%–11.3%, respectively.<sup>[7-9]</sup>

Hepatitis D (hepatitis delta) is one of the viral hepatitis caused by the hepatitis D virus (HDV), that its clinical manifestation differs according to the mode of infection.<sup>[10]</sup> HDV is a ribonucleic acid virus (RNA virus), which can only cause infection in the attendance of HBV and worsen the pre-existing HBV-related liver disease.<sup>[11,12]</sup> Studies have shown that, in Iran, the prevalence of HDV varied from 0% to 19.7%.<sup>[13]</sup> It is noticeable that the prevalence of HBV/HDV coinfection has increased during the last decade in Iran.<sup>[13]</sup>

Also, it is reported that the prevalence of hepatitis G virus (HGV) in patients undergoing hemodialysis is very high. The overall HGV prevalence in the patients undergoing hemodialysis is varied from 1.3% to 55%.<sup>[14]</sup> In 35% of patients with acute hepatitis with unknown etiology, the HGV RNA is detected. This proportion in chronic cases is about 39%. In patients with hepatitis C contamination and in multiple blood–transfused patients, HGV prevalence estimated as 21% and 58%, respectively.<sup>[15]</sup> Since the studies newly started, considering HGV in Iran, it is necessary to continue complimentary studies especially in high-risk patients undergoing hemodialysis.<sup>[15]</sup>

Human herpesvirus-8 (HHV8), known as Kaposi's sarcoma-associated herpes virus (KSHV), is accepted to be the infectious cause for Kaposi sarcoma.<sup>[16]</sup> In Iran, compared with blood donors (2%), a striking higher seroprevalence of HHV8 among hemodialysis (16.9%), renal transplant recipients (25%), and HIV (45.7%) patients has been reported. Results showed that a high prevalence of HHV8 infection in several at-risk groups, such as hemodialysis, renal transplant, and HIV-positive patients, needs more attention.<sup>[17]</sup> As another considerable infection, the inflammatory condition of HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).<sup>[18]</sup>

The tumor virus infections of HTLV-I, KSHV, and particularly, hepatitis viruses (HBV plus HCV) are prevalent

in hemodialysis patients, which might be detected as an important health concern specialty in mobile population.<sup>[19]</sup>

Considering the high prevalence of viral oncogenic infections in hemodialysis patients, two recently systematic reviews published on the prevalence of hepatitis B and hepatitis C in the Iranian hemodialysis patients.<sup>[5,6]</sup> We have yet to face with lack of comprehensive systematic review on other oncogenic viral infections in Iranian hemodialysis patients. This study aimed to review systematically all available documents on the prevalence of HEV, HGV, HTLV, HIV, and KSHV in Iranian hemodialysis patients.

## Methods

With the aim of estimation of the prevalence of oncogenic viral infections in Iranian hemodialysis patients, we conducted a systematic review of the literature and evidence. Since the studied factors are very numerous and there is even a high heterogeneity in each factor, so the meta-analysis was not performed.

## Study question

The study population was the Iranian hemodialysis patients. The interested outcome defined as presence of oncogenic viral infections through detecting the antibody in blood samples of target population confirmed by any of used blood tests.

## Search strategy

According to a systematic approach and using Medical Subject Headings<sup>[20]</sup> terms, Emtree, and related equal Persian key words for Iranian databases, the relevant literature searched is concentrating on “oncogenic viral infections,” “hepatitis D virus,” “hepatitis E virus,” “hepatitis G virus,” “Human herpes virus,” “human immunodeficiency virus,” “acquired immunodeficiency syndrome,” “hemodialysis patients,” and “renal transplantation,” in adult hemodialysis patients, living in Iran. There was no restriction for age, time of publication, and language of documents.

Searches run through main international databases of PubMed and NLM Gateway (for MEDLINE), Institute of Scientific Information (ISI), and Scopus. The domestic databanks of Barakat knowledge network system, Scientific

Information Database (SID) and Iran-doc also searched by English key words and the equal Persian key words.

Moreover, in the electronic data sources, we found 42 national, regional, and international Iranian medical science-related congresses from related gray literature. We also searched the research projects of 11 out of 53 Iranian universities of medical sciences from their websites. The references and citations of relevant articles were also assessed.

### Quality assessment and data extraction

This systematic review included all relevant cross-sectional studies, which have conducted in Iranian hemodialysis patients. The quality of studies assessed based on CASP tools.<sup>[21]</sup> There was not any restriction in terms of age and gender of the participants or jobs or type of background diseases, which need to be treated by hemodialysis.

Data were extracted through a check list, which was recording citation, publication year, study year, place of study, type of study, population, total sample size, mean age, type of measure, results of measures, and other information. All process of search and data extraction was followed by two independent research experts (Kappa statistic for agreement for quality assessment; 0.92) and probable discrepancy between them resolved based on third expert opinion.

### Statistical analysis

Prevalence of oncogenic viral infections in Iranian hemodialysis patients presented with 95% confidence interval (CI). Chi-square-based  $Q$ -test and  $I$ -square statistics used to assess the heterogeneity between studies of reported prevalence. The result of  $Q$ -test was regarded to be statistically significant at  $P < 0.1$ .

### Ethical considerations

Protocol of study was approved by the ethical committee of Alborz University of Medical Sciences. All of 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 oncogenic viral infections among Iranian hemodialysis patients. Based on our search strategy through comprehensive searching, 509 studies were found. From them, 314 articles were from international data bases and others from Iranian data banks. For more data availability, we also searched the reference list of related papers. After excluding duplicates and overlapping studies, 41 studies were included in the analysis [Figure 1].

Considering the results, 11 studies were relevant to HIV,<sup>[1,4,22-30]</sup> 10 studies assigned to HEV,<sup>[1,4,7,8,14,31-33]</sup>

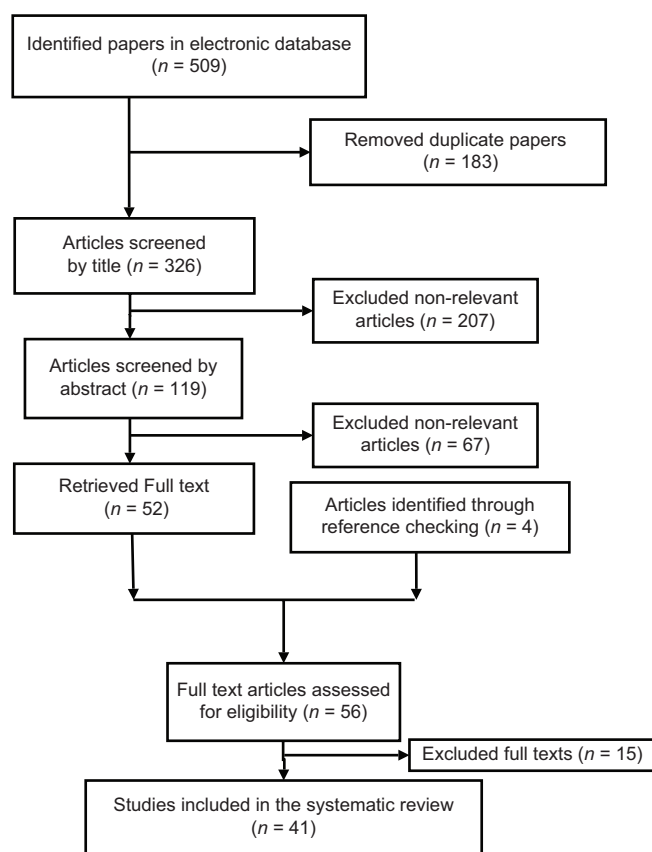


Figure 1: Papers' search and review flowchart for selection of primary study

and 7 studies belonged to HGV field.<sup>[14,24,28,34-38]</sup> The HDV,<sup>[14,22,25,26,39]</sup> HTLV1,2,<sup>[19,25,40,41]</sup> and KSHV<sup>[16,19]</sup> were the other research subject areas. Results of Chi-square test and  $I$ -square statistics for heterogeneity showed that reported prevalence is heterogamous between studies ( $I^2 = 100\%$  and  $P$  value  $< 0.001$ ); therefore, meta-analysis was not performed to estimate pooled prevalence

All of searched articles were in English or Persian language. Based on the geographical distribution, three studies were designed at national level and rests of them were at provincial levels. For one study, the study's level was not defined. Retrieving articles were assigned to studies conducted between 1990 and 2015. Regarding the mean age of patients, the maximum and the minimum levels were, respectively,  $62.16 \pm 14.86$  and  $35 \pm 13.15$  years old. The number of studied patients varied from 31 to 2,630 in different studies. The total number of study population in the selected studies in which the prevalence of oncogenic viral infection in HD had been investigated in various areas of Iran was 8,900, out of which 4,172 cases of HIV, 1,622 cases of HEV, 364 cases of HDV, 1,739 cases of HGV, 615 cases of HTLV1,2, and 388 cases of KSHV were found.

Moreover, along with the general specifications of studies and outcome measures, we have also included measures information. Considering the systematic review results, from 11 studies relevant to HIV in HD patients, 6 of the studies

**Table 1: The results of including papers' oncogenic viral infections in the hemodialysis patients of Iran**

Citation	Study year	Place of study	Total sample size	Mean (SD) age	SD age	Type of virus	kit	Prevalence (%)	95% CI
Mahdavamazdeh, (2009)	2005	Tehran,	2630	53.4	ND	HIV	ELISA	0.10	0.09-0.10
Keyvani (2013)	1975	IRAN	103	60.5	14.1	HIV	ELISA	0	0
Masood (2014)	2010	Birjand	41	54.93	16.46	HIV	ND	0	0
Rafiei (2011)	ND	Mazandaran	31	39.55	13.15	HIV	ND	0	0
Zahedi (2012)	2010	Kerman	228	51	9.5	HIV	ELISA	0	0
Bahri (2016)	2015	Bandar Abbas	153	54.06	15.68	HIV	ELISA	0	0
Aghasadeghi (2013)	2011	Tehran	120	55	16	HIV	ELISA	1.50	1.36-1.63
Eini (2015)	2010	Hamedan	153			HIV	ELISA	0	0
Dadmanesh (2015)	2012-2013	Tehran	138	62.16	14.86	HIV	PCR	0	0
Roushan (2015)	2012-2014	Mazandaran	482	54.96	16.1	HIV	PCR	0	0
Mobaiei (2013)	2011	Zanjan	93	57	18.5	HIV	ND	0	0
Eslamifar (2007)	2006	IRAN	77	52.1	16.7	HGV	ELISA	3.89	3.46-4.31
Mohsenzadeh (2012)	ND	ND	62	52.6	19.75	HGV	ELISA	24.19	21.86-26.51
Kheirabad (2016)	2015	Bandar Abbas, Hormozgan	149	56.23	12.35	HGV	ELISA	0	0
Mojahedi (2015)	2009	Mashhad	132	49.7	16.6	HGV	ELISA	0	0
Dadmanesh (2015)	2012-2013	Tehran	138	62.16	14.86	HGV	PCR	4.30	3.94-4.65
Samarbaf-Zadeh (2015)	ND	Khuzestan	516	ND	ND	HGV	ELISA	7.36	7.05-7.66
Samarbaf-Zadeh (2015)	ND	Khuzestan	516	ND	ND	HGV	RT-PCR	3.14	3.006-3.273
Kelishadi (2014)	2012	Gorgan	149	56	15.92	GBV-C	RT-PCR	14.7	13.67-15.72
Masood (2014)	2010	Birjand	41	54.93	16.46	HDV	ELISA	0	0
Keyvani (2013)	1975	IRAN	103	60.5	14.1	HDV	ELISA	36.7	34.41-38.98
Aghasadeghi (2013) <sup>[4]</sup>	2011	Tehran	120	55	16	HDV	ELISA	2.50	2.27-2.72
SirusJedary (2010)	2006-2007	Tabriz	100	ND	ND	HDV	ELISA	8	7.26-8.73
Pourahmad (2009) <sup>[31]</sup>	2007	Jahrom	43	59.3	14.4	HEV	ELISA	7	6.01-7.99
Zekavat (2013)	2010	Jahrom and Shiraz	80	55.69	14.70	HEV	ELISA	6.3	60.39-65.61
SeyedSeifollah Beladi Mousavi (2014)	ND	Ahvaz	47	55.27	8.1	HEV	ELISA	10.6	9.22-11.98
Alavian (2015)	2012	Isfahan	274	59.9	16.4	HEV	ELISA	28.30	27.07-29.52
Khoshbaten (2003)	2004	Tabriz	324	53.5	15.1	HEV	ND	7.4	7.01-7.78
Eini (2015)	2010	Hamedan	153	ND	ND	HEV	ELISA	19.20	17.94-20.45
Mobaiei (2013)	2011	Zanjan	93	57	18.5	HEV	ND	26.90	24.86-28.93
Taremi (2004)	2004	Tabriz	324	53.5	15.1	HEV	ELISA	7.4	7.02-7.78
Kelishadi (2014)	2012	Gorgan	149	56	15.92	HEV	RT-PCR	10.73	9.94-11.51
Ghaffari J (2013)	2011	Sari and Ghaemshahr	160	59.1	14.7	HTLV1	ELISA	0.6	0.55-0.64
Khameneh (2008)	2005-2006	Urmia	95	34	ND	HTLV I/II	ELISA	2.6	2.34-2.85
Khameneh (2008)	2005-2006	Urmia	49	34	ND	HTLV	western blot	14.3	12.54-16.05
Ghezeldasht (2015)	2009-2010	KhorasanRazavi	135	ND	ND	HTLV-I	PCR	5.9	5.42-6.37
Masood (2014)	2010	Birjand	41	54.93	16.46	HTLV11/2	ELISA	2.43	2.05-2.80
Ghezeldasht (2015)	2009-2010	Mashhad	135	ND	ND	HTLV I	PCR	70.40	68.19-71.80
Ghezeldasht (2015)	2009-2010	KhorasanRazavi	135	ND	ND	KSHV	PCR	3.0	2.74-3.25
Ghezeldasht (2015)	2009-2010	Mashhad	135	ND	ND	KSHV2	PCR	3.0	2.74-3.25
GharehBaghian (2006)	2005	Tehran	118	ND	ND	KSHV	ELISA	16.9	15.60-18.19

ELISA=Enzyme-linked-immunosorbent antibody; PCR=Polymerase chain reaction; HIV=Human immunodeficiency virus; HEV=Hepatitis E virus; HDV=Hepatitis Delta virus; HGV=Hepatitis G virus; HTLV I, II=Human T-lymphotropic virus Type I, II; KSHV=Kaposi's sarcoma-associated herpesvirus; ND=Not determined

were reported based on enzyme-linked-immunosorbent antibody (ELISA) as an HIV infection-detecting method and 2 studies used polymerase chain reaction (PCR) method. The methods were not mentioned for the rest of the studies [Table 1]. The HIV prevalence in hemodialysis

patients was between 0% and 1.5%; the highest prevalence was seen in Tehran [Table 1].

Also, out of nine studies related to prevalence of HGV, five of the studies were reported based on ELISA as an HCV infection-detecting method. Rest of studies considered

other methods, such as PCR (four studies) [Table 1]. The HGV prevalence in hemodialysis patients was between 0% and 24.19%, the negative prevalence was observed in Mashhad, and the place of the highest prevalence was not mentioned [Table 1].

Furthermore, from four studies related to HDV in HD patients, ELISA as detecting method was used for all. The HDV prevalence in HD patients was reported between 0% in Birjand and 36.7% in national level. Also, from 10 studies related to HEV, 6 studies used ELISA method for detecting infections, 2 studies used PCR, and the rest not mentioned. The results of the included articles showed that the prevalence of HEV varied from 7.4% in Tabriz province to 63% in HD patients in Shiraz and Jahrom. In addition, the studies related to HTLV I-II, three studies used ELISA, two studies used PCR, and one study used western blot as detecting method of infections. From three studies related to KSHV, two studies used PCR and the rest used ELISA method. The results of the included articles showed that the prevalence of HTLV I and KSHV varied from 0.6% in Sari and Ghaemshar to 70.4% in Mashhad, 3% in Mashhad, and 16.9% in Tehran province in hemodialysis patients.

Qualitative data assessment of the included articles showed that the prevalence of oncogenic viral infections among Iranian hemodialysis patients in Iran is rather high in some areas and the prevalence of HIV in HD patients in most of areas of Iran is negative and various in different areas of Iran.

## Discussion

Of these 41 studies, 11 studies were relevant to HIV, 10 studies assigned to HEV, and 7 studies belonged to HGV field. The HDV, HTLV1, and KSHV were the other research subject areas. As a considerable point, we found a wide limitation in data presentation. Most of the papers did not explicitly reveal the demographic characteristics of the study groups. There is also a clear lack of explanation for measurement tools and requires details of research methods.

The prevalence of HIV and HGV in hemodialysis patients, respectively, ranged from 0% to 1.5% and 0% to 24.19% in different provinces. The prevalence of HTLV<sub>1</sub> in hemodialysis patients ranged from 0.6% to 70.4% in different provinces, which show relatively high prevalence of this virus. The study of Khamenei *et al.* also confirmed the high prevalence of this virus in hemodialysis patients and emphasized that these patients should be screened for HTLV and positive cases should be isolated.<sup>[42]</sup>

Since a global distribution has been considered for hepatitis E virus infection, in this study, the prevalence of HEV in hemodialysis patients was reported 6.3% in Shiraz to 28.3% in Isfahan. According to the study of Belady *et al.*, the prevalence of HEV was 10.63% among this group of patients and there was no association between HEV, age,

gender, duration of hemodialysis, and HCV antibody titer.<sup>[32]</sup> Zekavat, his research team, referring to the absence of this virus in hemodialysis patients, emphasized that use of safety precautions could be practical way for better prevention.<sup>[43]</sup>

The study by Santos in 2017 showed that overall prevalence of HTLV-1 infection in a sample of maintenance of hemodialysis patients was similar to that of other viral infections (2.48%), such as hepatitis B and C.<sup>[44]</sup> The related study performed according to the 2006 census on the northeast of Iran showed that it was an endemic area for HTLV-I infection since 1996.<sup>[45,46]</sup>

The estimation in deferent population is different, but most of the investigation emphasizes on the need to prompt attention for prevention and control of emerging increasing of infections.<sup>[19,47-49]</sup>

Patients with end-stage renal diseases need to be dialyzed via blood or peritoneal ways that poses them to meet blood-borne infections.<sup>[2]</sup> These processes make them more susceptible to infectious diseases and even the wide category of noncommunicable diseases, such as cancer.

The results of investigations confirm that in patients with acquired immunodeficiency syndrome (AIDS) or who involve in solid organ recipients, the risk of cancer increased. As another considerable point, the blood-borne infections discussed as the common causes of cancers in humans.<sup>[19]</sup> The accelerating trends of related extracted cancer become the leading cause of death especially in developing countries where they cited as the second cause of death.<sup>[49,50]</sup> According to the international agency estimation on cancer, it is estimated that the incidence of cancer continues to rise as a cause of 13.1 million deaths by 2030.<sup>[47,51]</sup>

In most of the countries, comparing with the general population, the prevalence of oncogenic viral infections in the end-stage renal disease patients show higher considerable levels.<sup>[50]</sup> Recent evidence has the special emphasis on KSHV in northeast of Iran.<sup>[19]</sup>

These viruses' infections considered as health priorities from different aspects of preventive strategies that discuss as curable medications or vaccines for preventing KSHV, HCV, and HTLV-I infections and also the probability of coinfection with other tumor viruses that are very important problems in immune compromised patients. These points lead to the priority of oncogenic viruses' infections.<sup>[49,50]</sup>

Considering the previous efforts in this line, this study benefitting from many strengths. This is a comprehensive systematic review on prevalence of oncogenic viral infections in the Iranian hemodialysis patients that included all available data of qualified studies. We systematically searched related international databases. As the main

limitation, the validity of our results depends on the quality of the primary studies that are included. On the other hand, heterogeneity of searched results limits the generalization of our findings.

## Conclusion

This is the comprehensive systematic review on oncogenic viral infection prevalence in the Iranian hemodialysis patients. Present findings emphasize on requirement to evidence-based practical intervention for better prevention and control of problem. The findings could be used as scientific evidence for developing related policies and highlighting the future plan of complementary researches.

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## Conflicts of interest

There are no conflicts of interest.

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