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REVIEW

Epidemiology of hepatitis E virus in Iran

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Abstract

Iran is known as an endemic country for hepatitis E virus (HEV) infection, while there are variations in the epidemiology of HEV infection throughout the country. The available epidemiological studies in different regions of Iran show HEV seroprevalence of 1.1%-14.2% among general population, 4.5% -14.3% among blood donors, 6.1%-22.8% among injecting drug users, 6.3%-28.3% among hemodialysis patients, 1.6%-11.3% among patients infected with other hepatitis viruses, 27.5% among patients with chronic liver disease, 30.8% among kidney transplant recipient patients, and 10%-16.4% among human immunodeficiency virus-infected patients. These variations reflect differences in the status of public health and hygiene, risk factors, and routes of transmission in different regions and groups. Therefore, it is necessary to review the epidemiology of HEV infection to determine the most prevalent risk factors and routes of transmission, and to evaluate the effectiveness of preventive strategies employed in the public health services of the country. Moreover, the other epidemiological aspects of HEV, including the genotypic pattern, extra hepatic manifestations, and incidence of chronic infection need to be investigated among Iranian population to expand the current knowledge on the epidemiology of HEV and to clarify the real burden of HEV infection. Therefore, this review was performed to provide a general overview regarding the epidemiology of HEV in Iran.

Key words: Hepatitis E virus; General population; Blood donors; Injecting drug users; Hemodialysis; Immunocompromised patients; Chronic liver disease; Prevalence; Epidemiology; Iran

Core tip: Iran is considered as an endemic country for hepatitis E virus (HEV) infection, while there are variations in the epidemiology and prevalence of hepatitis E throughout the country. These variations reflect differences in the life styles, status of public health, risk factors, and routes of transmission in different groups and geographical regions of Iran.

Therefore, this study was conducted to review the epidemiological aspects of HEV infection in Iran.

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INTRODUCTION

Hepatitis E virus (HEV) is the causative agent of hepatitis E infection[1]. This infection is usually asymptomatic or acute self-limiting[1] but might lead to fulminant hepatitis or even long-term chronic infection and cirrhosis with a high rate of mortality due to severe liver failure in high-risk groups, such as pregnant women, organ transplant recipient patients, immunocompromised patients, and those with pre-existing liver problems[1-6]. HEV is predominantly transmitted *via* the fecal-oral route; however, transmission of HEV through blood transfusion, organ transplantation, hemodialysis, placenta and sexual intercourse is also possible[1,7,8]. Among these, sexual transmission of HEV is less common and has mostly been reported in homosexual males[7,9].

HEV is a small spherical virus with a positive-sense RNA genome and an icosahedral non-enveloped capsid[5,10-12]. The viral genome contains three partially overlapping open reading frames[5,13,14]. HEV has been classified into the family *Hepeviridae*, the genus *Orthohepevirus*, and the species *Orthohepevirus A*[1,15]. There are four genotypes of HEV capable of causing human infection with different epidemiological features[3,16]. These genotypes have further been subdivided into 24 subgenotypes[5,17,18]. Genotypes 1 and 2 are only recognized in human beings, while genotypes 3 and 4 are found in domestic and wild animals as well[7,19-21]. Despite this genetic heterogeneity, only one serotype has been recognized so far[1,5,22].

HEV genotypes differ in their severity, pathogenecity, mortality rates, mode of transmission, age distribution, and geographical distribution[1,7-9,23]. HEV genotype 1 is frequently found in North Africa and Asia[9]. HEV genotype 2 is more common in West Africa and Mexico[7,9]. HEV genotype 3 is considered to have a worldwide distribution and is more prevalent in several European and American countries, as well as Japan, China, Australia, and New Zealand[7,9,10]. HEV genotype 4 has been reported in Asian countries and more recently in Central Europe[5,9,23]. Genotypes 3 and 4 appear to be less virulent than genotypes 1 and 2[1,24]. HEV genotype 1 is associated with the most cases of fulminant hepatitis and high mortality during pregnancy[8,10]. While HEV genotype 3 is the cause of almost all cases of chronic HEV infections worldwide[5,7,8]. Infection with HEV genotype 4 seems to be asymptomatic and mostly remains undiagnosed[6,9].

Hepatitis E is usually an asymptomatic or acute self-limited infection and only requires supportive care. However, when fulminant or chronic hepatitis arises, therapeutic intervention is an obligation[9,10]. Reduction of immunosuppressive therapy is considered as the first-line therapy in immunocompromised patients with chronic HEV infection. Nevertheless, at the same time, it can increase the risk of graft rejection[3,5,9,25-27]. In such conditions, organ transplant recipient patients benefit most from antiviral therapy, including pegylated interferon (peg-IFN) monotherapy or combination therapy with ribavirin and peg-IFN[3,10,25].

These antiviral agents are associated with severe side effects. IFN-therapy may result in acute graft rejection[3,5,8,25]. Ribavirin administration induces severe hemolytic anemia; and when the dose of ribavirin is reduced, the viral clearance is not achieved[8]. Therefore, the combination of ribavirin with a reduction in the doses of immunosuppressive drugs has been found to be the most promising treatment option[5,10,25]. In addition, these antiviral drugs should be administered with caution during pregnancy due to their teratogenicity[10,27,28]. Early delivery of fetus or termination of pregnancy should be considered as another option to save mothers' lives[28,29]. Administration of the antiretroviral drugs in human immunodeficiency virus (HIV)-positive patients can result in an increase in the proportion of T helper cells and subsequently clearance of HEV infection[25].

Considering the side effects and limitations of the currently available treatment regimens as well as the absence of a specific antiviral treatment for HEV infection, preventive measures and vaccination against HEV infection are the most desirable approaches for controlling HEV infection[25,30]. HEV vaccines using the truncated forms of capsid protein have been evaluated in human clinical trials, and one of them, HEV 239 vaccine, has been approved in china in 2011. Although this vaccine has shown promising results, it is not commercially available worldwide[5,20,27,31]. Therefore, preventive measures are still known to be the best option. Providing clean drinking water supplies, improving the hygienic infrastructure and sanitary status, washing hands and vegetables properly, boiling drinking water, and avoiding consumption of undercooked foods and unpeeled fruits are some of these preventive measures[1,5,11,23,31,32]. In addition, proper chlorination of water supplies, sanitary preparation of food, and public awareness regarding the possible routes of HEV transmission are essential to reduce the risk of exposure to HEV in the community[1,11,23].

HEV has infected one-third of the world's population[13,17]. In addition, 20 million new cases and 3.3

million acute cases of HEV infection occur globally each year[3,33], and HEV-related hepatic failure is responsible for approximately 56600 deaths per year[33,34]. The mortality rate of HEV infection is 1%-2% in the general population[17], but it may rise to 10%-25% in pregnant women[7,20] and over 75% in individuals with pre-existing liver problems[20].

HEV is a considerable global health concern. Although HEV infection was traditionally believed to be limited to developing countries, currently it is known that this infection has a worldwide distribution with different epidemiological patterns[9]. In developing countries where the infection is endemic, acute outbreaks or large epidemics of hepatitis E occur due to contamination of water supplies mainly at the time of heavy rainfall or following floods. These outbreaks are largely due to genotypes 1 and 2 and more frequently affect young adult males[1,3,5,8,9,18]. Whereas in developed countries, HEV infection is non-endemic and mostly occurs as sporadic locally-acquired disease due to consumption of contaminated food supplies. The infection is due to genotypes 3 and 4 and predominantly found among middle-aged elderly males throughout the year[1,3,5,9,18].

Apart from variations in the global epidemiological patterns of HEV, there is a wide range of variation in the prevalence and epidemiology of HEV infection within a country[5,16,35,36]. These variations reflect differences in the lifestyle, status of public health, risk factors, and routes of transmission in different regions and groups[35-37]. It is therefore necessary to review the epidemiology of HEV infection to determine the most prevalent risk factors and routes of transmission and to evaluate the effectiveness of prevention strategies employed in the public health services of a country. These epidemiological studies are not only essential for improving the current strategies to minimize the risk of acquiring HEV infection in the society but also clarify the real burden of HEV infection.

This study has the objective to review the epidemiology of hepatitis E in Iran, a vast country located in the Middle East, with an extension of about 1700000 km^2 and an estimated population of 70 million inhabitants in different provinces with various ethnicities[38].

HEV IN GENERAL POPULATION

With an overall prevalence rate of more than 5% in the general population, Iran is considered as an endemic country for HEV infection[36,39]. However, the seroprevalence of hepatitis E in the general population varies considerably in different parts of the country, ranging from 0.0% to 0.9% for anti-HEV IgM and 1.1% to 14.2% for anti-HEV IgG and the total HEV antibodies in different studies[35,39-46] (Table 1[35,39-46]). Differences in the lifestyles, risk factors, levels of exposure, the geographic regions, study population, study periods, sample sizes, time of sampling, and the diagnostic accuracy of kits used to determine anti-HEV antibodies in various studies can explain these variations[35-37]. However, the role of public health services, hygienic conditions, socioeconomic status, and environmental factors should not be dismissed[36,37,42].

The predominant mode of transmission in Iran is fecal-oral route, especially feces-contaminated drinking water; however, the other routes of transmission might also have a minor role in the spread of HEV but with undetermined importance[35,43,47]. Food-borne transmission of zoonotic origin is unlikely, since wild animal hunting and swine farming are prohibited in Iran[35]. Person-to-person transmission is most likely rare in Iran, since no association between the household size and seroprevalence rate of HEV has been reported[42]. Overall, the importance of the other probable routes of transmission in spread of HEV infection in the society still requires to be determined.

Despite the epidemiological pattern in developing countries, where HEV most often affects young adults[1,5,9], the seroprevalence rate in Iran increases with age due to cumulative exposure to HEV over time with the highest prevalence rate among middle-aged and elderly individuals aged over 50 years[35,36,40,41,45]. Another possible reason is improvement in public hygiene, sanitation, sewage disposal and drinking water supply systems, which has resulted in decreased prevalence of HEV infection in young population of the country over time[36,47].

Except two reports[44,45], in the majority of studies, the seroprevalence of HEV was higher in females compared to males. However, none of these differences were significant[35,36,39-42]. In rural areas, inhabitants were more likely to be positive for HEV serological markers compared to individuals living in urban areas[39,43]. Appropriate access to the public health services, sewage disposal systems, and safe water supplies in cities can explain these differences in the seroprevalence rates regarding the place of residence[35,37,43]. Taken together, in studies from Iran, socioeconomic status, level of sanitation, population density, age, level of education, and place of residency were found to be risk factors for acquiring HEV infection in the society[35,42,43,48].

In one study from Iran, the prevalence of anti-HEV IgG antibody in the general population was as high as 46.1% in South-West of the country[36]. The reason of this high endemicity is most likely Karun River as the drinking water source of the inhabitants, where the city sewage is also discharged in. It is also worthy to note that the participants in the mentioned study were all adults, mostly middle-aged and elderly adults[36]. Iran is located in the Middle East between HEV high endemic countries on the eastern and western borders. This considerable geographic location has affected epidemiological pattern of HEV infection in Iran[35,47].

A few occasional waterborne outbreaks of hepatitis E have also occurred in Iran[47]. The first documented outbreak was reported in Kermanshah city, West of

Table 1 Seroprevalence of hepatitis E virus in different population groups in Iran

Study population	City or province	Location	Year of study	No. of participants	Age, mean ± SD (age group), yr	No. of positive cases	HEV seroprevalence	HEV diagnosis	Manufacturer of Serology kits	Ref.
General population	Nahavand	West	2003	1824	34.7 ± 19.5 (6 to > 70)	170	9.3%	Anti-HEV IgG	DIA.PRO, Italy	Taremi *et al*[42]
General population	Sari, Mazandaran	North	2003	1080	2 to 25	25	2.3%	Anti-HEV IgG	DIA.PRO, Italy	Saffar *et al*[43]
General population	Tehran and Golestan	North-Center North-East	2006	1423	37.9 ± 13.4 (18 to 65)	105	7.4%	Anti-HEV total antibodies	DIA.PRO, Italy	Sepanlou *et al*[39]
General population	Shiraz	South	2011-2012	1030	< 1 to 95	138	13.4%	Anti-HEV total antibodies	DIA.PRO, Italy	Asaei *et al*[40]
						9	0.9%	Anti-HEV IgM		
General population	Mashhad	North-East	2009	1582	29.06 ± 18.513 (1 to 90)	225	14.2%	Anti-HEV total antibodies	DIA.PRO, Italy	Ahmadi Ghezeldasht *et al*[35]
General population	Isfahan	Center	2005	816	6 to > 50		3.8%	Anti-HEV total antibodies	DIA.PRO, Italy	Ataei *et al*[41]
General population	Tehran	North-Center	2006-2007	551	41.28 ± 16.96 (1 to 83)	51	9.3%	Anti-HEV IgG	DIA.PRO, Italy	Mohebbi *et al*[44]
General population	Ahvaz	South-West	2014	510	45.89 ± 14.63 (18 to 81)	235	46.1%	Anti-HEV IgG	DIA.PRO, Italy	Farshadpour *et al*[36]
						7	1.4%	Anti-HEV IgM		
General population	Khorramabad	West	2009	400	36 (> 20)	31	7.8%	Anti-HEV total antibodies	(ND)	Raoofi *et al*[45]
Soldier	Tehran	North-Center	2006	800	19 ± 1.2 (17 to 23)	9	1.1%	Anti-HEV IgG	DIA.PRO, Italy	Ghorbani *et al*[46]
							0.0%	Anti-HEV IgM		
Blood donor	Khuzestan	South-West	2005	400	33.3 (18 to 60)	46	11.5%	Anti-HEV IgG	HEV-EIA, Biokit, Spain	Assarehzadegan *et al*[55]
Blood donor	Tehran	North-Center	2003-2004	90	31.8 ± 11	7	7.8%	Anti-HEV total antibodies	DIA.PRO, Italy	Aminiafshar *et al*[54]
Blood donor	Tabriz	North-West	2004	399	31.4 ± 9.8	31	7.8%	Anti-HEV IgG	DIA.PRO, Italy	Taremi *et al*[49]
Blood donor	Markazi	West-Center	2012	530	36.3 ± 11.7 (18 to 71)	76	14.3%	Anti-HEV IgG	DIA.PRO, Italy	Ehteram *et al*[53]
Blood donor	Kerman	South-East	2007-2008	400	20 to 60	31	7.7%	Anti-HEV IgG	DIA.PRO, Italy	Arabzadeh *et al*[52]
Blood donor	Tehran	North-Center	2014	559	38 (18 to > 47)	45	8.1%	Anti-HEV IgG	DIA.PRO, Italy	Hesamizadeh *et al*[50]
Blood donor	Tehran	North-Center	ND	200	20 to 61	9	4.5%	Anti-HEV antibodies	DRG, Diagnostics, Germany	Keyvani *et al*[51]
Drug users (addicts)	Hamadan	West	2011-2012	131 (IDUs)	35.57 ± 8.13 (22 to 70)	8	6.1%	Anti-HEV IgG	DIA.PRO, Italy	Keramat *et al*[58]
				131 (non-IDUs)	31.57 ± 8.19 (20 to 45)	2	1.5%			
Drug users	Ahvaz	South-West	2005-2006	228	34.1 ± 6.1 (18 to 54)	35	15.4%	Anti-HEV IgG	DIA.PRO, Italy	Alavi *et al*[57]
				114 (IDUs)		26	22.8%			
				66 (Inhalant)		6	9.1%			
				48 (Oral opiate)		3	6.2%			
Hemodialysis	Hamadan	West	2010	153	< 20 to > 60	30	19.2%	Anti-HEV IgG	DIA.PRO, Italy	Eini *et al*[63]
Hemodialysis	Tabriz	North-West	2004	324	53.5 ± 15.1	24	7.4%	Anti-HEV IgG	DIA.PRO, Italy	Taremi *et al*[64]
Hemodialysis	Jahrom	South	2007	43	59.3 ± 14.4	3	7.0%	Anti-HEV IgG	DIA.PRO, Italy	Pourahmad *et al*[65]
Hemodialysis	Zanjan	West	2011	93	57.0 ± 18.5 (16 to 88)	25	26.9%	Anti-HEV total antibodies	DIA.PRO, Italy	Mobaien *et al*[66]
Hemodialysis	Jahrom and Shiraz	South	2010	80	55.69 ± 14.70 (26 to 80)	5	6.3%	Anti-HEV IgG	DIA.PRO, Italy	Zekavat *et al*[67]
Hemodialysis	Ahvaz	South-West	ND	47	55.27 ± 8.1	5	10.6%	Anti-HEV IgG	DIA.PRO, Italy	Beladi Mousavi *et al*[68]
Hemodialysis	Isfahan	Center	2012	274	59.9 ± 16.4 (21 to 80)	78	28.3%	Anti-HEV IgG	DIA.PRO, Italy	Alavian *et al*[69]
HCV-infected patients	Tehran	North-Center	ND	100	20 to 61	7	7%	Anti-HEV antibodies	DRG, Diagnostics, Germany	Keyvani *et al*[51]
HBV-infected patients	Tehran	North-Center	ND	150	20 to 61	17	11.3%	Anti-HEV antibodies	DRG, Diagnostics, Germany	Keyvani *et al*[51]
Thalassemia patients with chronic hepatitis C	Iran	Iran	2009-2010	64	25.08 ± 6.46 (12 to 76)	1	1.6%	Anti-HEV IgG	DIA.PRO, Italy	Karimi Elizee *et al*[56]

Hemophilia patients with chronic hepatitis C	Iran	Iran	2009-2010	155	30.63 ± 11.51 (12 to 76)	5	3.2%	Anti-HEV IgG	DIA.PRO, Italy	Karimi Elizee *et al*[56]
GB Virus C positive hemodialysis patients	Gorgan	North-East	2012	22	54.32 ± 12.56	0	0.0%	total anti-HEV	DIA.PRO, Italy	Kelishadi *et al*[77]
patients with chronic liver disease	Azerbaijan	North-West	2005-2006	200	48.26 ± 18.19 (10 to 87)	55	27.5%	Anti-HEV IgG	DIA.PRO, Italy	Somi *et al*[78]
HIV-infected patients	Tehran	North-Center	2012	100	38	10	10%	Anti-HEV IgG	DIA.PRO, Italy	Ramezani *et al*[79]
						0	0.0%	Anti-HEV IgM		
						0	0.0%	HEV RNA		
HIV-infected patients	Shiraz	South	2013	158	39.1 ± 8	26	16.4%	Anti-HEV total antibodies	DIA.PRO, Italy	Joulaei *et al*[80]
Kidney transplant recipient patients	Urmia	North-West	1991-2010	91	35.4 ± 14.5 (6 to 65)	28	30.8%	Anti-HEV IgG	DIA.PRO, Italy	Rostamzadeh Khameneh *et al*[81]

ND: Not defined; HEV: Hepatitis E virus.

Iran, in 1991. At the same time, a suspected outbreak was reported in Isfahan province, during which over 100 inhabitants were infected in Fereidon-Shahr. Another outbreak occurred in Lordegan, Southwest of Iran, in 1999 and affected 154 people[45,47]. The history of these outbreaks clearly implies that HEV infection is not new to Iran, and probability of future outbreaks in the country should be considered and preventive strategies for controlling transmission of HEV infection should be provided.

The prevalence rate of HEV infection in the general population is likely underestimated due to the lack of adequate population-based studies, asymptomatic nature of HEV infection, and the fact that hepatitis E is not a reportable infection in the public health system of Iran. In addition, the incidence and case fatality rate of hepatitis E in the general population of Iran are unclear and need further investigation.

HEV IN BLOOD DONORS

Even though HEV infection is an old enterically transmitted disease, it is also considered an emerging transfusion-transmitted infection[4,7]. Since only recently, HEV has been recognized as a threat to blood safety[4,6]. The possibility of HEV transmission through blood transfusion dates back to 2002 and 2004, when two molecular studies in Japan introduced HEV as a transfusion transmissible virus[6,7,18]. Since then, several studies from Japan, the United Kingdom, France, and Saudi Arabia have confirmed HEV transmission through blood transfusion[6,7,18,23].

These studies have reported high prevalence of anti-HEV antibodies, and viral RNA among blood donors[6,23]. Donor-recipient linked studies have also confirmed transmission of HEV to blood transfusion recipients[6,7]. In addition, higher incidence of hepatitis E in multi-transfused individuals compared to controls suggests this transmission[7,18,23]. Moreover, the high rate of asymptomatic or undiagnosed infection among blood donors increases the risk of HEV transmission[7,18,23]. Fortunately, these unnoticeable infections are preventable through screening of blood donations for HEV infection. Screening methods are based on the detection of anti-HEV antibodies and HEV RNA in serum or plasma samples of blood donors[1,4,7,8,16,18].

The presence of elevated liver enzymes and HEV RNA in blood is short lived, and becomes normalized or undetectable approximately 6 weeks and 3 weeks after the onset of clinical illness, respectively[5,7,16]. In some instances, viremia may persist for a longer period, especially in children after acute hepatitis E[4,7]. In addition, HEV RNA has been detected up to 3 years in immunocompromized patients, especially those with renal transplantation[4]. IgM increases during the acute phase of infection and becomes undetectable after 3-8 mo[16]. While IgG appears after the increase of IgM level and persists for years with unknown duration[5,8,16]. Therefore, anti-HEV IgG positive samples in the absence of IgM and HEV RNA are defined as past HEV infection. While a positive anti-HEV IgM test can be indicative of current

infection if HEV RNA is detected[1,16]. Some patients in viremic phase of infection do not show anti-HEV IgM responses[49]. Majority of risks are due to the presence of HEV RNA in blood of apparently healthy donors with normal levels of liver enzymes and negative anti-HEV IgM, which is indicative of asymptomatic viremia[7,18]. In these instances, blood transfusion is capable of trasmitting HEV infection despite negative serological markers. Therefore, HEV is a potential threat to blood safety[7,18].

Since 2005, Japan has implemented HEV RNA testing of all donors along with screening for elevated liver enzymes levels[7]. While some other countries perform selective HEV screening for high-risk recipients[8]. The necessity to screen all blood donations or at least a part of them for HEV infection needs to be considered in Iran.

Studies on the seroprevalence of HEV in blood donors are limited in Iran and mainly have been conducted in main cities, while the seroprevalence varies from 4.5% to 14.3% in these studies[49-55] (Table 1[49-55]). Despite this high prevalence, screening of blood donors for HEV is not performed in the blood banks of Iran until more evidence becomes available regarding the potential threat of HEV to blood safety[49,53]. In addition, the risk of incidence and transmission of hepatitis E by blood transfusion in Iran is unknown. Since the studies in Iran have only reported the rate of seropositivity, which is incapable of estimating the rate of viremic blood donors[49,53]. Therefore, additional studies to investigate the possibility of HEV transmission through blood transfusion seem to be necessary. Even if the risk of transmission through blood transfusion is low, we should not neglect the importance of this infection. Since HEV causes serious consequences in high-risk recipients, who often require blood transfusion. Therefore, access to HEV-free blood and blood products is the highest priority for this group of patients[4,7,18,50].

The seroprevalence of HEV among hemophilia and thalassemia patients in Iran is lower than expected and is in the range of that found in the general population of Iran[56]. The reason of this low prevalence may be that the blood donor population in Iran has mostly been consisted of young individuals, while HEV mostly affects middle-aged or old population in Iran[49,50,54]. This suggests that blood transfusion may not be a risk factor for transmission of HEV infection among hemophilia and thalassemia patients in Iran[56]. Still, more studies are required to confirm this issue.

HEV IN INJECTING DRUG USERS

With having approximately 180000 injecting drug users (IDUs) among Iranian adults aged 15-64 years, Iran is considered one of the countries with the highest numbers of injection drug users in the world[38]. While only two studies have assessed the possible effect of injecting drug use on the seroprevalence of HEV among IDUs in Iran[57,58]. Alavi *et al*[57] reported high seroprevalence of HEV in IDUs (22.8%) compared to inhalant drug users (9.1%) and oral opiate drug users (6.2%) and suggested an association between injection drug abuse and HEV seropositivity in Ahvaz in 2005-2006. While some other studies from France, the United States (US), and Denmark have rejected this association[59-62]. Keramat *et al*[58] reported high prevalence of HEV in IDUs (6.1%) compared to non-IDUs control group (1.5%) and found no relationship between duration of injection and HEV seroprevalence in Hamadan in 2011-2012.

These studies indicated high seroprevalence of HEV infection among IDUs in Iran[57,58], while this seroprevalence was not influenced by the type of substance abused but was associated with the route of administration[57]. According to the results of these studies, IDUs in Iran are at risk of acquiring HEV infection most likely due to exposure to infected blood through sharing syringe[58]. As a result, injection drug use was proposed as a possible route of HEV transmission. However, still more investigations are required to confirm this issue.

HEV IN HEMODIALYSIS PATIENTS

The seroprevalence of hepatitis E among patients on maintenance hemodialysis (HD) varies considerably from 4% to 28.3% in different cities of Iran[63-69] (Table 1[63-69]). The reason of this vast geographic variation in different HD centers is unknown, but it may be due to the different levels of safety strategies in HD units, as well as the public health and prevalence of HEV infection in the community[30,64,69]. In some studies, HEV seroprevalence in HD patients is lower than or in the range of HEV seroprevalence in the general population of Iran[64,65,67], indicating a low risk of exposure to HEV in these areas or maybe a negligible HEV transmission in HD centers. While in some other studies, it is noticeably higher than HEV seroprevalence in the general population, which may be indicative of parenteral transmission of HEV infection[30,63,66,69]. Similar high prevalence of anti-HEV antibodies in HD patients has been reported in Egypt (22.9%)[70], Japan (30%)[71], and Turkey (20.6%)[72]. In contrast, reports from Italy (6.0%)[73], Brazil (6.2%)[74], and Spain (6.3%)[75] have indicated a low seroprevalence of HEV among HD patients.

The seroprevalence of HEV infection among Iranian HD patients was associated with almost no risk factor in most of these studies[63,64,67,68]. While duration of HD was significantly associated with HEV seropositivity in two studies[65,69]. In addition, in one study, 41.7% of HEV seropositive HD patients had a history of blood transfusion[69]. These studies support the nosocomial transmission of HEV infection[30,47,65]. While the others indicate a rare acquisition of HEV infection through hemodialysis[64,67]. Overall, the epidemiology of HEV infection among HD patients in Iran seems to be

a controversial issue due to these variations in the results of so far conducted studies. Therefore, more extensive or comprehensive studies in different geographical regions of Iran are required to resolve these conflicts between the results and to determine the exact epidemiological pattern of HEV infection among HD patients.

Considering the clearance of a significant level of anti-HEV antibodies during the process of dialysis as well as weak antibody responses due to chronic renal disease, a considerable proportion of HEV seropositive HD patients may be reported as seronegative[30,67,69,76-81]. Except one study[65], the serum levels of liver enzymes were normal or low in HEV seropositive patients on maintenance hemodialysis due to the fast reduction of these enzymes to the normal levels[30,67]. Therefore, some HEV-infected HD patients may remain undiagnosed. These HD patients with inapparent HEV infection might be the main source of HEV transmission as a nosocomial infection in HD units[30]. Overall, neither anti-HEV antibodies nor level of liver enzymes can be valid diagnostic markers in case of HEV infection among HD patients[30]. Therefore, serious safety measures and proper screening of HD patients for hepatitis E in HD centers should be considered to prevent transmission of HEV during the process of hemodialysis.

HEV IN PATIENTS INFECTED WITH OTHER HEPATITIS VIRUSES

Viral hepatitis infections are believed to be associated with an increased risk of hepatitis E occurrence, and co-infection or superinfection with HEV will enhance the risk of liver failure[11,17,82,83]. In recent years, several studies have reported high prevalence of hepatitis E among patients with chronic viral hepatitis and supported the possibility of parenteral transmission of HEV[30,82,84], while other studies have demonstrated a low occurrence of these co-infections or superinfections and found no association between HEV and other viral hepatitis[85,86]. This variation in the prevalence of HEV among patients with other viral hepatitis reflects differences in the routes of transmission and distribution of these hepatotropic viruses in different parts of the world. Although HEV is predominantly transmitted *via* the fecal-oral route, the possibility of parenteral transmission has also been reported in endemic countries[82,87].

Currently, only a few reports are available regarding the prevalence of HEV infection among patients with viral hepatitis in Iran. Keyvani *et al*[51] reported high prevalence of anti-HEV antibody in HBV (11.3%) and HCV (7%)-infected patients compared to healthy blood donors (4.5%) in Tehran. In another study by Karimi Elizee *et al*[56], the seroprevalence of HEV among thalassemia and hemophilia patients with chronic hepatitis C was reported to be 1.6% and 3.2%, respectively, which is similar to HEV seroprevalence in Iranian general population. Kelishadi *et al*[77] reported the absence of anti-HEV IgG antibody in GB virus C positive hemodialysis patients in Gorgan. These studies were unable to determine the effect of hepatitis E on the clinical outcomes of the other viral hepatitis. Overall, data concerning dual infection with hepatitis E and the other viral hepatitis in Iran are scarce, and the routes of HEV transmission in this group of patients are unclear. Therefore, further studies are required to determine the association between HEV and other viral hepatitis in Iran.

HEV IN IMMUNOCOMPROMISED AND IMMUNOSUPPRESSED PATIENTS

HEV infection in immunocompromised and immunosuppressed patients may lead to chronic hepatitis E, with an increased risk of developing liver fibrosis and cirrhosis, and subsequently lower survival of the infected patients[9,10,27]. Chronic HEV infection is characterized by the persistent presence of detectable HEV-RNA in serum and stool for more than 6 mo (more than 3 mo in organ transplant recipient patients) along with persistently elevated liver enzymes[3,5,8,9,33]. So far, chronic hepatitis E has been observed in HIV-infected patients, organ transplant recipient patients, and those with hematological malignancies, who receive anticancer chemotherapy[5,10,25-27,88]. However, the possibility of HEV chronicization in other patients with immunosuppressive conditions is currently under investigation, and this chronic infection may identify in more categories of patients in near future[3].

More recently, some cases of chronic HEV infection have also been observed in elderly immunocompetent individuals[8]. While no report of chronic infection has been documented in pregnant women and infants[16,28]. Almost all cases of chronic hepatitis E have been observed following infection with HEV genotype 3[3,5,7,25]. The first case of chronic hepatitis E caused by HEV genotype 4 has recently been identified in a Chinese patient[3,9].

The seroprevalence of hepatitis E among organ transplant recipient patients varies from 2.3% to 43.9% in different studies[5]. While the prevalence of HEV infection based on the detection of viral RNA ranges from 0.9% to 3.5%[5]. This prevalence among transplant recipient patients with elevated liver enzymes is 4.3%-6.5%[5]. The chronicity rate of hepatitis E is approximately 60% in organ transplant recipient patients without therapeutic interventions[25,26,30].

Indeed, progression to chronicity in immunocompromised patients could be mediated by inability to clear the virus after acute infection, which is related to the degree of immunosupression and immunological status of transplant recipient patients at the time of HEV infection as well as the time period between the transplantation and incidence of HEV infection[3,5,10,29].

Therefore, suboptimal HEV-specific cellular immune responses, low lymphocyte and platelet counts, the occurrence of HEV infection immediately after transplantation, and the use of more effective immunosuppressive drugs such as tacrolimus are risk factors for the incidence of chronic hepatitis E in immunocompromised patients following exposure to HEV[1,3,5,26,88]. Even the presence of anti-HEV IgG antibodies prior to re-exposure to HEV cannot exclude the chance of reinfection in transplant recipient patients, and such reinfections may lead to chronic infection[3]. The main route of HEV transmission in immunocompromised patients seems to be fecal-oral, especially *via* consumption of contaminated food[3,5,16]. However, acquisition of HEV infection following blood transfusion and liver transplantation is also possible but seems to be uncommon[3,5,26]. Most patients with chronic hepatitis E are asymptomatic, and the rest show nonspecific symptoms, including fatigue, fever, abdominal pain, asthenia, and very rarely jaundice[5,25]. Chronic hepatitis E can rapidly progress to liver fibrosis, cirrhosis, and subsequently fatal liver failure in immunocompromised patients[3,5,25]. In addition, numerous hepatitis E-associated extrahepatic manifestations, including neurological, hematological, musculoskeletal, renal manifestations, as well as acute pancreatitis, autoimmune thyroiditis, myocarditis, mixed cryoglobulinemia, thrombocytopenia, arthralgia, Henoch-Schonlein purpura, myasthenia gravis, haemolysis, membranous glomerulonephritis associated with immunological disorders and many others have been reported in patients with acute or chronic HEV infection[7,9,25,33,89,90].

Such extrahepatic complications sometimes outshine clinical manifestations of hepatic injury, and the causative agents, hepatitis E, might not be suspected. Therefore, the probability of hepatitis E in extrahepatic manifestations should be considered[33].

Chronic hepatitis E results in graft loss and subsequently retransplantation in organ transplant recipient patients. However, recurrent hepatitis E and subsequently progressive chronic infection after retransplantation may also occur if the viral clearance is not achieved before retransplantation[5].

In this situation, early diagnosis of hepatitis E in this group of patients is the highest priority. The diagnosis should be based on the detection of HEV RNA in serum, cerebrospinal fluid (CSF) in case of neurological complications or stool samples, not levels of liver enzymes and results of serological tests[3,26,33,91]. Since various factors can elevate liver enzymes, including drugs, toxin, graft rejection, infections, and biliary tract dysfunction[30]. Furthermore, the presence of chronic HEV infection in organ transplant recipient patients is sometimes accompanied by normal liver enzymes[30]. In addition, the delay or absence of seroconversion and loss of anti-HEV antibodies are frequently observed in this group of patients due to immunosuppressive conditions, which result in suppression of antibody development over time[5,91]. Therefore, immunocompromised or immunosuppressed patients with chronic HEV infection may have normal liver enzymes and negative serological tests[26,30,81].

In these conditions of uncertainty, the awareness of physicians regarding chronic HEV infection is crucial. Since most cases of chronic HEV infection may be missed due to the lack of HEV consideration among physicians or inappropriate choose of diagnostic assays[3,25].

Reports on HEV prevalence in immunocompromised patients in Iran are scarce. Rostamzadeh Khameneh *et al*[81] assessed the seroprevalence of HEV among 91 Iranian kidney transplant recipient patients. Overall, the seroprevalence of HEV was 30.8%. Joulaei *et al*[80] reported a HEV seroprevalence of 16.4% among 158 HIV-infected individuals in Shiraz in 2013. In another study by Ramezani *et al*[79], the seroprevalence of HEV infection was found to be 10% among 100 HIV-positive individuals in Tehran in 2012. These limited studies were unable to determine the incidence and prevalence of chronic HEV infection among immunocompromised patients in Iran. Since only the seroprevalence of anti-HEV IgG antibodies has been assessed, while HEV-RNA has not been measured in these studies[81,88]. Therefore, more studies are required to gain insight into the burden of chronic HEV infection in Iran.

CONCLUSION

However, Iran is classified as an endemic region for HEV infection, but we do not know much about this infection in Iran. The available epidemiological data have demonstrated the seroprevalence of HEV infection in different groups and regions of Iran, while the presence of HEV-RNA has not been evaluated in the studies published so far. In addition, the distribution pattern of HEV genotypes is unknown in Iran.

From historical aspect, hepatitis E is not new in Iran but is underestimated due to the lack of awareness amongst physicians and inappropriate diagnosis of the infection. The importance of HEV infection as a main public health problem cannot be neglected any longer. The identification of HEV-associated extrahepatic manifestations and chronic hepatitis E in immunocompromised patients has attracted attention to the study of HEV in recent years. While these new aspects of so thought acute self-limited hepatitis remain unknown in Iran. Overall, still a long way is ahead to determine the epidemiological patterns of HEV in Iran. To approach this goal, further epidemiological investigations at the national level are needed to more clearly delineate the incidence and prevalence of HEV infection in Iran. In addition, nationwide efforts should be pursued to control and prevent HEV infection in Iran.

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