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TOPIC HIGHLIGHT

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Epidemiology of hepatitis C virus in Iran

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Abstract

In Iran, the prevalence of hepatitis C virus (HCV) infection is relatively low according to the population-based epidemiological studies. However, the epidemiology of HCV is changing and the rate of HCV infection is increasing due to the growth in the number of injecting drug users in the society. In addition, a shift has occurred in the distribution pattern of HCV genotypes among HCV-infected patients in Iran. Genotype 1a is the most prevalent genotype in Iran, but in recent years, an increase in the frequency of 3a and a decrease in 1a and 1b have been reported. These variations in the epidemiology of HCV reflect differences in the routes of transmission, status of public health, lifestyles, and risk factors in different groups and geographic regions of Iran. Health policy makers should consider these differences to establish better strategies for control and prevention of HCV infection. Therefore, this review was conducted to present a clear view regarding the current epidemiology of HCV infection in Iran.

Key words: Hepatitis C virus; Blood donors; Injecting drug users; Hemodialysis; Hemophilia; Thalassemia; Genotypes; Occult hepatitis C virus; Epidemiology; Iran

Core tip: The distribution patterns of hepatitis C virus (HCV) infection are related to different status of public health and the presence of risk factors in the society. In Iran, the predominance of risk factors for transmission of HCV has changed from blood transfusion to intravenous drug use; and due to the growth in the number of injecting drug users, the prevalence of HCV infection is rising in the country. Even the recent changes in the distribution pattern of HCV genotypes confirm this issue. Overall, the epidemiology of HCV is

changing in Iran. Therefore, this review was conducted to present a clear view about current epidemiology of HCV in Iran.

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INTRODUCTION

Hepatitis C virus (HCV) is a small, enveloped positive-stranded RNA virus, belonging to the family *Flaviviridae* and the genus *Hepacivirus*[1,2]. Based on genomic heterogeneity, HCV has been classified into seven genotypes and over 70 different subtypes[3,4]. HCV is transmitted through exposure to infected blood and blood products. Blood transfusion, injecting drug use, sexual intercourse, surgery, and tattooing are some possible ways to spread HCV infection[5,6]. Among these, HCV transmission by sexual intercourse is less common and includes those that lead to mucosal exposure to infectious blood or blood-derived body fluids and is related to the presence of mucosal tears and genital ulcerative disease[7,8].

HCV is the major cause of chronic liver disease, and can lead to cirrhosis and hepatocellular carcinoma (HCC)[3,9]. Although the infection is preliminary acute with a wide spectrum of clinical manifestations from asymptomatic to mild or even severe clinical illness[10], about 75% to 85% of acute HCV infections slowly progress to chronic infection[11]. Approximately 10%-20% of those chronically infected are at risk of developing liver cirrhosis within 20 to 30 years, and of those with cirrhosis, 1%-5% per year will develop HCC[12].

HCV infection is defined as the presence of HCV-RNA and anti-HCV antibodies in serum or plasma. A positive HCV antibody test [enzyme linked immunosorbent assay (ELISA) and immunoblot assay] indicates exposure to HCV, however, it cannot distinguish between current or past infection. In general, anti-HCV antibody positive samples can be defined as current HCV infection if the HCV RNA test [reverse transcriptase polymerase chain reaction (RT-PCR)] is positive[8,13].

According to the World Health Organization reports, about 130-150 million of the world population have chronic HCV infection[14]. In addition, 3-4 million new cases of HCV infection emerge globally each year[15,16]. The chronic infection might result in cirrhosis, hepatic failure, or HCC, which are responsible for approximately 350000 to 500000 deaths per year[5,14,17,18]. Therefore, HCV is a life threatening global health problem, and its prevention is the main objective.

HCV has a high rate of genetic heterogeneity, therefore, no vaccine or immunoglobulin exist to prevent this infection[18]. Recent advances in HCV therapy have led to the development of new antiviral drugs for treatment of HCV infection, including the protease inhibitors telaprevir, simeprevir, boceprevir, and paritaprevir; NS5A inhibitors ledipasvir, daclatasvir, and ombitasvir; the nucleotide analog NS5B polymerase inhibitor sofosbuvir; and the non-nucleotide polymerase inhibitor dasabuvir[8,19,20]. These new therapies are well-tolerated and safer and much more effective than the previous therapies pegylated interferon (IFN)/ribavirin[20]. Despite these advantages, pegylated IFN-α in combination with ribavirin is recommended as the standard treatment for HCV infection in Iran[21-24]. The reasons for this are the high cost and restricted availability of the new medications in low- and middle-income countries[25].

Iran is a vast country with various ethnicities in different provinces. This country, with an area of about 1700000 km^2, is located in the Middle East between Arab peninsula, Indian subcontinent, Europe, and Middle Asia[26,27]. There are variations in the prevalence and epidemiology of HCV in different groups and regions throughout the country. To achieve better strategies for the prevention and management of HCV infection, the current knowledge regarding the epidemiology of HCV infection merits reviewing. Therefore, we present here a clear review about the current epidemiology of HCV in Iran.

HCV IN BLOOD DONORS

In Iran, the prevalence of HCV infection among blood donors in different studies varies considerably, depending on the study population, sample sizes, study periods, the geographic regions, risk factors, and the methods and type of kits used to determine HCV[15,28]. According to the results of a meta-analysis study, the prevalence of anti-HCV among 10739221 blood donors was 0.5% during 1996 to 2011[28]. In another study, the rate of anti-HCV seropositivity among 6499851 blood donors was 0.13% during 2004 to 2007[29]. The highest anti-HCV prevalence of 1.39% was declared in 2005, followed by a significant decreasing rate from 0.13% in 2007 to 0.03% in 2009[4,28]. The reasons for this decline were the implementation of more restrictive rules in physical examination prior to donation and the application of more sensitive HCV test kits for screening the blood by Iran Blood Transfusion Centers[27,28]. In addition, the public has become more aware of the routes of transmission of HCV infection in recent years[29].

Iran has the lowest anti-HCV prevalence among blood donors compared to corresponding figures in the Middle East countries, such as 0.6% in Lebanon, 0.8% in Kuwait, 0.9% in Oman, 2.7% in Yemen, and 5%-25% in Egypt[4,27,28,30,31]. Globally, however, the lowest HCV prevalence of 0.01%-0.1% has been reported in the

Table 1 Prevalence of hepatitis C virus among blood donors in Iran

Author	Year of study	City or province	Location	No. of participants	No. of positive samples	Prevalence	Test	Ref.
Taheri Azbarmi	2003-2005	Rasht, Gilan province	North	49820	91	0.18%	ELISA and RIBA	[36]
Mansour-Ghanaei	1998-2003	Gilan	North	221508	3603	1.62%	ELISA	[37]
					709	0.32%	RIBA	
Bani Aghil	2006-2008	Golestan	North-East	128198	161	0.12%	ELISA and immunoblot	[38]
Khedmat	2003-2005	Tehran	North-Center	1004889	21390	2.10%	ELISA	[39]
					1005	0.10%	RT-PCR	
Attarchi	2003-2004	Tehran	North-Center	26645	42	0.20%	ELISA and RIBA	[40]
Khedmat	2005-2006	Tehran	North-Center	318029	323	0.09%	ELISA, immunoblot and RT-PCR	[35]
Bozorgi	2002-2004	Qazvin	West-Center	48116	73	0.15%	ELISA and RIBA	[41]
Mahdaviani	2004	Arak	West-Center	11615	81	0.70%	ELISA	[42]
					33	0.20%	RIBA	
Bozorgi	2009	Qazvin	West-Center	20591	328	1.59%	ELISA	[43]
					35	0.17%	HCV confirmatory tests (ND)	
Afzali	1996-2001	Kashan	Center	43731	477	1.10%	ELISA	[44]
Moniri	2001-2002	Kashan	Center	600	3	0.50%	ELISA	[45]
Karimi	2004-2006	Shahr-e Kord	Central	35124	70	0.20%	ELISA and immunoblot	[46]
Masaeli	2002-2003	Isfahan	Center	29458	24	0.27%	ELISA and RIBA	[47]
Esmaieli	2006-2007	Bushehr	South	20294	42	0.20%	ELISA and immunoblot	[48]
Ghavanini	1998	Shiraz	South	7897	47	0.59%	ELISA and immunoblot	[49]
Emamghorashi	2001-2003	Jahrom	South	3000	9	0.30%	ELISA and immunoblot	[50]
Kasraian	2002-2005	Shiraz	South	507531	710	0.14%	ELISA	[51]
Kasraian	2007-2008	Shiraz	South	93987	203	0.21%	ELISA and RIBA	[52]
Delavari	2003	Kerman	South-East	15252	60	0.39%	ELISA	[53]
Tajbakhsh	2004	Shahr-e kord	West	11472	69	0.60%	ELISA	[54]
Doosti	2003-2004	Shahrekord	West	11200	76	0.67%	ELISA	[55]
						0.59%	immunoblot	
						0.41%	RT-PCR	
Ghafouri	2006-2009	South Khorasan	East	42652	31	0.07%	ELISA	[56]
					13	0.03%	RIBA	

ND: Not defined; ELISA: Enzyme linked immunosorbent assay; RT-PCR: Reverse transcriptase polymerase chain reaction; RIBA: Recombinant immunoblot assay.

United Kingdom and Scandinavia[5,18,32-34].

At present, the ELISA and confirmatory recombinant immunoblot assay (RIBA) are used routinely for screening of the blood donors by the Iranian blood bank transfusion centers. It seems screening of blood is an important factor in controlling and reducing the rate of HCV infection in the general population. However, the presence of asymptomatic or occult HCV infected donors with no detectable HCV Ab or low copy number of HCV genomes in their blood is a potential source of HCV transmission. Thus, the risk of HCV transmission through blood transfusion is considered an important public health concern[28,35] (Table 1[35-56]).

HCV IN GENERAL POPULATION

With an overall anti-HCV prevalence of less than 1% in the general population, Iran is considered a country with low frequency HCV infection[27]. However, it seems the prevalence of HCV is slightly rising in the country[57,58]. The prevalence of HCV infection in the general population varies considerably in different regions of Iran (Table 2[58-68]). These variations in the prevalence of HCV might be due to the differences in the quality of public health services, lifestyles, habits, and rates of high-risk behaviors in different geographic regions[15,28].

In Iran, the prevalence of HCV infection in the general population is lower than those of the neighboring countries such as Afghanistan (1.1%), Turkey (1%-2.1%), Pakistan (4.7%), Iraq (7.1%), and Qatar (6.3%)[4,30]. Globally, the highest HCV prevalence of 17.5% (13%-22%) has been reported in Egypt[59].

The general population-based prevalence of HCV infection is used to describe and compare the local and global epidemiology of HCV infection[10,16]. The surveys on prevalence of HCV in the blood donor population fail to assess the true prevalence in an entire community. Since a large number of HCV positive cases are excluded from donating blood, the donor population is representative of a population at low risk of HCV infection. A recent study reported a HCV prevalence of 9.2% in the excluded individuals[27]. Therefore, the prevalence of HCV in the general population is higher than that in the donor population[27,28].

HCV IN HIGH-RISK GROUPS

HCV in intravenous drug users

Presently, injecting drug use is the main route of HCV

Table 2 Prevalence of hepatitis C virus among general population in Iran

Author	Year of study	City or province	Location	No. of participants	No. of positive samples	Prevalence	Test	Ref.
Zamani	2008-2011	Amol, Mazandaran	North	6145	12	0.20%	ELISA	[60]
					5	0.08%	RIBA	
					3	0.05%	RT-PCR	
Mansour-Ghanaei	2003	Gilan	North	383	9	2.30%	ELISA	[61]
					5	1.30%	RT-PCR	
Shakeri	2010-2011	Mashhad	North-East	3870	8	0.20%	ELISA	[62]
					5	0.13%	RT-PCR	
Ghadir	2006	Golestan	North-East	2123	56	2.60%	ELISA	[63]
					22	1.00%	RIBA	
Merat	2006	Golestan	North-East	1895	18	1.00%	ELISA and RIBA	[58]
Merat	2006	Tehran	North-Center	2326	8	0.30%	ELISA and RIBA	[58]
Merat	2006	Hormozgan	South	1463	24	1.60%	ELISA and RIBA	[58]
Motlagh	2001	Ahvaz	South-West	80	5	6.25%	ELISA	[64]
					0	0.00%	Immunoblot	
Nikbakht	2007-2008	Ahvaz	South-West	712	9	0.63%	ELISA	[65]
Moradi	2001-2002	Saravan, Sistan and Baluchestan	South-East	365	3	0.80%	ELISA	[66]
Sayad	2006	Kermanshah	West	1721	15	0.87%	ELISA, immunoblot and RT-PCR	[67]
Mohebbi	2007-2008	Lorestan	West	827	2	0.20%	ELISA	[68]

ELISA: Enzyme linked immunosorbent assay; RT-PCR: Reverse transcriptase polymerase chain reaction; RIBA: Recombinant immunoblot assay.

Table 3 Prevalence of hepatitis C virus among injecting drug users in Iran

Author	Year of study	City or province	location	No. of participants	No. of positive samples	Prevalence	Test	Ref.
Mohtasham Amiri	2003	Gilan	North	81	72	88.9%	ELISA	[72]
Rahimi-Movaghar	2006-2007	Tehran	North-Center	895	309	34.5%	ELISA	[73]
Hosseini	2006	Tehran	North-Center	417	334	80.0%	ELISA	[74]
Zali	1995	Tehran	North-Center	402 (Male imprisoned IDUs)	182	45.3%	ELISA, RIBA	[75]
Zamani	2004	Tehran	North-Center	202	105	52.0%	Particle Agglutination (PA) assay	[76]
Hajinasrollah	2005	Tehran	North-Center	65	11	17.0%	ELISA	[77]
Amin-Esmaeili	2006-2007	Tehran	North-Center	895	309	34.5%	ELISA	[78]
Nokhodian	2008-2009	Isfahan	Center	531	250	47.1%	ELISA	[79]
Zamani	2008	Isfahan	Center	117	71	60.7%	EIA	[80]
Kassaian	2009	Isfahan	Center	943	392	41.6%	ELISA	[81]
Fadaei Nobari	2011	Isfahan	Center	1747	595	34.0%	ELISA	[82]
Sofian	2009	Arak, Markazi	West-Center	153 (Male IDUs)	91	59.5%	ELISA	[83]
Ramezani	2012	Arak	West-Center	100 (Male IDUs)	56	56.0%	ELISA	[84]
Honarvar	2012-2013	Shiraz	South	569 (High risk groups)	109	19.1%	ELISA and immunoblot	[70]
				233 (IDUs)	94	40.3%		
				336 (non-IDUs)	15	4.4%		
Davoodian	2002	Bandar Abbas, Hormozgan	South	249	163	64.8%	ELISA	[85]
Sarkari	2009-2010	Kohgiloyeh and Boyerahmad	South-West	158	67	42.4%	ELISA	[86]
Imani	2004	Shahr-e Kord	Sout-West	133	15	11.3%	ELISA	[87]
Alavi	2002-2006	Ahvaz	South-West	333	103	30.9%	ND	[88]
Mohammad Alizadeh	2002	Hamadan	West	149 (IDUs Prisoners)	47	31.5%	ELISA, immunoblot	[89]
Keramat	2005-2007	Hamadan	West	379 (High risk groups)	135	35.6%	ELISA, immunoblot	[90]
				199 (IDUs)	126	63.3%		

IDUs: Injecting drug users; ND: Not defined; ELISA: Enzyme linked immunosorbent assay; RIBA: Recombinant immunoblot assay.

transmission[6,9,69]. Iran has one of the highest numbers of drug addicts in the world[9,70]. It has been reported that 2.8% of Iranian adults aged 15-64 years are drug abusers and about 180000 (12.2%) of this population are injecting drug users (IDUs)[9]. Estimates from Iran show a HCV prevalence of 50%-75% among IDUs[6].

Table 4 Prevalence of hepatitis C virus among hemodialysis in Iran

Author	Year of study	City or province	Location	No. of participants	No. of positive samples	Prevalence	Test	Ref.
Makhlough	2006	Mazandaran	North	186	39	21.0%	ELISA	[99]
					21	11.3%	RT-PCR	
Amiri	2001	Gilan	North	298	80	26.8%	ELISA	[100]
					74	24.8%	Immunoblot	
Joukar	2008	Gilan	North	514	61	11.9%	ELISA	[101]
					32	6.2%	RT-PCR	
Samimi-rad	2005	Markazi	West-Center	204	11	5.4%	ELISA, RIBA and RT-PCR	[102]
Bozorghi	2006	Qazvin	West-Center	89	9	10.3%	ELISA	[103]
					6	6.4%	RIBA	
Somi	2012	Tabriz	North-West	455	37	8.1%	ELISA	[104]
Zahedi	2010	Kerman	South-East	228	16	7.0%	ELISA	[105]
					7	3.0%	PCR	
Kalantari	2010-2011	Isfahan	Center	499	26	5.2%	ELISA	[106]
Zamani	1998–2005	Amol, Tonekabon, Rasht and Ramsar Mazandaran and Gilan provinces	North	334	67	20.0%	ELISA, RT-PCR	[107]
Assarehzadegan	2005-2006	Khuzestan	South-West	214	34	7.9%	ELISA, RT-PCR	[108]
Nemati	1990-2006	Tehran	Center	112	6	5.3%	ELISA, RT-PCR	[109]
Sotoudehjahromi	2006	Jahrom	South	34	3	8.8%	ELISA	[110]
					2	5.9%	RIBA	
Alavian	2003	Tehran	North-Center	838	176	21.0%	ELISA	[111]
					111	13.2%	RIBA	
Broumand	2002	Tehran	North-Center	548	105	19.6%	ELISA	[112]
					51	9.33%	RT-PCR	
Nasiri-Toosi	2007	Tehran	North-Center	130	11	8.5%	ND	[113]
Mohammad-Alizadeh	2002	Hamedan	West	96	9	11.4%	ELISA	[114]
Saboor	1999-2000	Kermanshah	West	140	37	26.4%	ELISA	[115]
Jabbari	2008	Golestan	North-East	93	23	24.7%	ELISA, RIBA	[116]
Ansari	2005-2006	Urmia	North-West	50	19	38.0%	EIA	[117]
					12	24.0%	RT-PCR	
Hassanshahi	2006-2007	Kerman	South-East	203	64	31.5%	ELISA, RT-PCR	[118]
Ansar	1997-1998	Gilan	North	93	52	55.9%	ELISA	[119]

ND: Not defined; ELISA: Enzyme linked immunosorbent assay; RT-PCR: Reverse transcriptase polymerase chain reaction; RIBA: Recombinant immunoblot assay.

However, the prevalence of anti-HCV among IDUs varies considerably in different regions of Iran (Table 3[70-90]). The outcomes revealed that Gilan, Hamedan, Tehran, and Hormozgan provinces have the highest rate of HCV infection, while Shahre Kord had the lowest rate of infection (Table 3). As a result, IDUs are the main source of HCV infection in Iran and account for the large proportion of current HCV transmission in the society[6,9,27]. In addition, the prevalence of HCV infection in prisons of Iran is extremely high, where 38% to 90% of imprisoned IDUs have been infected with HCV[9]. Interestingly, tattooing more effectively transmits HCV infection than injecting drug use among Iranian prisoners[6].

The global prevalence of HCV infection among IDUs varies considerably from 9.8% to 97.4%[71]. Approximately 10 million IDUs with a global midpoint prevalence of 67% are positive for anti-HCV. The highest rate of HCV infection among the IDUs has been reported in China (67%, 1.6 million), the United States (73.4%, 1.5 million), and Russia (72.5%, 1.3 million)[71].

HCV in hemodialysis patients

Distribution of HCV infection among hemodialysis patients has a vast geographic variation in different regions of Iran (Table 4[91-119]). According to a recent meta-analysis study in Iran, prevalence of HCV infection among this group of patients was reported to be 13.6%, 12.2%, and 7.6% by ELISA, RIBA, and PCR, respectively, which is lower than those of Saudi Arabia (50.5%), Kuwait (43.4%), Jordan (32.5%), and Pakistan (23.7%)[91-94] but higher than those of Australia (2.3%), United Kingdom (2.7%), Germany (3.9%), and Bahrain (7.4%)[95-97]. The risk of HCV infection is extremely high among hemodialysis patients[11]. Recent surveys show that the prevalence of HCV infection among hemodialysis patients is not related to history of blood transfusion. Considering the fact that the length of time on dialysis is significantly associated with HCV seropositivity, the nosocomial transmission is the main route of HCV transmission

Table 5 Prevalence of hepatitis C virus among hemophilia patients in Iran

Author	Year of study	City or province	Location	No. of participants	No. of positive samples	Prevalence	Test	Ref.
Mansour-Ghanaei	1999	Gilan	North	101	72	71.30%	RIBA	[120]
Torabi	2004	East Azarbaijan	North-West	130	72	56.00%	ELISA, RIBA	[121]
Valizadeh	2010	West Azarbaijan	North-West	35	3	8.57%	ELISA, RIBA and RT-PCR	[122]
Mousavian	2003-2005	Tehran	North-Center	1095	802	72.30%	ELISA and RT-PCR	[123]
Kalantari	2008-2010	Isfahan	Center	615	495	80.50%	ELISA	[124]
					347	56.40%	RT-PCR	
Mobini	2006	Yazd	Center	77	41	53.20%	ELISA	[125]
					38	49.40%	RT-PCR	
Yazdani	1996-2010	Isfahan	Center	350	231	66.00%	ELISA	[126]
Javadzadeh Shahshahani	2003	Yazd	Center	74	36	48.60%	ELISA and RIBA	[127]
Samimi-Rad	2004	Markazi	West-Center	76	34	44.70%	ELISA	[128]
					33	43.40%	RIBA	
					23	30.26%	RT-PCR	
Mahdaviani	2004	Markazi	West-Center	68	26	38.20%	ELISA	[129]
					25	36.70%	RIBA	
Karimi	1999-2000	Shiraz	South	281	44	15.65%	ELISA and immunoblot	[130]
Assarehzadegan	2008-2009	Ahvaz	South-West	87	47	54.00%	ELISA	[131]
					42	48.30%	RT-PCR	
Zahedi	2002	Kerman	South-East	97	43	44.30%	ELISA and RIBA	[132]
Sharifi-Mood	2003-2006	Zahedan, Sistan and Baluchistan	South-East	81	24	29.60%	ELISA and immunoblot	[133]
Esfahani	2012	Hamadan	West	89	44	49.40%	ELISA	[134]
					15	16.70%	RT-PCR	

ELISA: Enzyme linked immunosorbent assay; RT-PCR: Reverse transcriptase polymerase chain reaction; RIBA: Recombinant immunoblot assay.

among Iranian hemodialysis patients[11,98].

HCV in hemophilia patients

Hemophilia patients may acquire HCV infection *via* contaminated blood products[98]. In Iran, the prevalence of HCV among hemophilia patients is very high, with an overall prevalence of 40.8%[98] and has a wide geographic variation (Table 5[120-134]). Most of the HCV infections among hemophilia patients are asymptomatic and may lead to liver failure. Therefore, routine screening for HCV infection in hemophilia patients is required to prevent the serious consequences of HCV infection[27].

HCV in thalassemia patients

HCV is a major cause of mortality in thalassemia patients due to post-transfusion HCV infection, which dramatically progresses to liver failure or even HCC[27,135]. Therefore, HCV infection is currently considered the main health problem in thalassemia patients, and much more attention to HCV screening in the blood transfusion process may improve survival of thalassemia patients[136]. Even though the current policies of blood banks have considerably decreased the incidence of HCV infection in thalassemia patients, blood transfusion remains the main risk factor for HCV infection among this group of patients because of transfusion of HCV-infected seronegative blood donated during the window period[27,136,137]. Therefore, the rate of HCV infection is high among thalassemia patients[137].

The geographical distribution of HCV infection among thalassemia patients varies widely in different regions of Iran (Table 6[86,118,119,127-129,137-151]), but a recent meta-analysis study reported the overall HCV prevalence is 18% among thalassemia patients in Iran[136]. Iran has the lowest rate of HCV infection among thalassemia patients in comparison with Eastern Mediterranean countries[136]. High prevalence of HCV infection has been reported among thalassemia in Egypt (69%), Saudi Arabia (63%), and Pakistan (45%)[136].

HCV in health care workers

Health care workers are at the risk of acquiring HCV infection due to occupational exposures to blood and blood-derived body fluids[152]. There are few reports on the prevalence of HCV infection among health care workers in Iran. In Shoaei *et al*[153], HCV infection status was negative in 203 health care workers in Isfahan city in 2012. Similarly, all 191 health care workers were tested negative for HCV antibodies in Shahrud province in 2010[154]. Hadadi *et al*[155] reported a HCV prevalence of 6.6% (31/467) among health care workers in Tehran in 2004-2005, and Sarkari *et al*[86] reported a HCV seroprevalence of 4.2% among 212 health care workers in Kohgiloyeh and

Table 6 Prevalence of hepatitis C virus among thalassemia patients in Iran

Author	Year of study	City or province	Location	No. of participants	No. of positive samples	Prevalence	Test	Ref.
Mirmomen	2002	Tehran	North-Center	410	80	19.6%	ELISA, RIBA	[138]
		Kerman	South-East	100	18	18.8%		
		Qazvin	West-Center	95	23	25.3%		
		Semnan	East-Center	81	19	24.4%		
		Zanjan	West	46	1	2.2%		
		Total		732	141	19.6%		
Ansar	1997-1998	Rasht	North	105	67	63.8%	ELISA	[119]
Ghane	2010-2011	Gilan and Mazandaran	North	245	46	18.8%	ELISA	[139]
					28	11.4%	Nested-PCR	
Tamaddoni	2005	Babol	North	113	12	10.6%	ELISA	[140]
Mansouritorghabeh	2007	Mashhad	North-East	360	30	8.33%	ELISA	[137]
Alavi	ND	Tehran	North-Center	90 (pediatric patients)	12	13.3%	ELISA, RT-PCR	[141]
Alavian	2002	Qazvin	West-Center	96	23	24.2%	ELISA, RIBA	[142]
Samimi-Rad	2004	Markazi	West-Center	98	7	7.1%	ELISA	[128]
					5	5.1%	RIBA	
					2	2.04%	RT-PCR	
Bozorgi	2005	Qazvin	West-Central	207	54	26.1%	ELISA	[143]
					50	24.01%	RIBA	
Azarkeivan	1996-2009	Tehran	North-Center	395	109	27.5%	EIA, RIBA	[144]
Mahdaviani	2004	Markazi	West-Center	97	9	9.2%	ELISA	[129]
					7	7.2%	RIBA	
Nakhaie	1999-2000	Tehran	North-Center	507	122	24.0%	ELISA	[145]
					41	8.1%	RT-PCR	
Kalantari	2008-2010	Isfahan	Center	545	50	9.1%	ELISA	[124]
					31	5.6%	RT-PCR	
Ataei	1996-2011	Isfahan	Center	466	37	8.0%	ND	[146]
Javadzadeh Shahshahani	2003	Yazd	Center	85	8	9.4%	ELISA, RIBA	[127]
Karimi	1999-2000	Shiraz	South	466 (pediatric patients)	73	15.7%	ELISA and immunoblot	[147]
Kashef	2006	Shiraz	South	131	24	18.3%	ELISA and immunoblot	[148]
					7	5.3%	RT-PCR	
Kadivar	1999	Shiraz	South	147	40	27.2%	ELISA	[149]
Shahraki	2005-2007	Zahedan	South-East	560 (pediatric patients)	30	5.3%	ELISA	[150]
					20	3.5%	PCR	
Hassanshahi	2006-2007	Kerman	South-East	181	81	44.7%	ELISA, RT-PCR	[118]
Ghafourian	2005-2006	Ahvaz	South-West	206	58	28.2%	ELISA	[151]
Boroujerdnia					46	22.3%	RT-PCR	
Sarkari	2009-2010	Kohgiloyeh and Boyerahmad	South-West	49	3	6.1%	ELISA	[86]

ND: Not defined; ELISA: Enzyme linked immunosorbent assay; RT-PCR: Reverse transcriptase polymerase chain reaction; RIBA: Recombinant immunoblot assay.

Boyerahmad province in 2009-2010.

The global prevalence of HCV infection among health care workers is 1%-6%[156]. After HBV, HCV is the most common blood-borne infection found among health care workers. Needle-stick or sharp injuries and mucosal exposure following blood splash are the most common risk factors for HCV infection among health care workers[152,153]. Therefore, prevention strategies and training programs are needed for health care workers to reduce the incidence of HCV infection in this group.

HCV in homeless people

Homeless people are one of the main high-risk groups for acquiring HCV infection because of high-risk behaviors, lifestyle, low levels of education, poverty, and poor hygiene[157,158]. There are over 100 million homeless people worldwide, and the prevalence of HCV infection among this group varies from 3.9% to 36.2% in different parts of the world[159]. Currently, there are no data on the number of homeless people in Iran, and only a few studies are available on the prevalence of HCV infection among homeless people in Tehran, the capital of Iran. Amiri *et al*[157] reported a HCV prevalence of 23.3% among 593 homeless individuals in Tehran in 2012. In another study by Vahdani *et al*[158], the prevalence of HCV infection was found to be 42.8% among 202 homeless men in Tehran city in 2007. According to the available data in Iran, the prevalence of HCV infection is considerably high among

Table 7 Prevalence of hepatitis C virus among HIV-positive patients in Iran

Author	Year of study	City or province	Location	No. of participants	No. of positive samples	Prevalence	Test	Ref.
Babamahmoodi	2008-2010	Mazandaran	North	80	27	33.8%	ELISA	[173]
Ramezani	1999-2004	Tehran	North-Center	95	65	68.0%	ELISA	[167]
SeyedAlinaghi	2004- 2005	Tehran	North-Center	201	135	67.2%	ELISA	[170]
Ataei	1998-2007	Isfahan	Center	130	100	77.0%	ELISA and RIBA	[168]
Davarpanah	2006-2007	Shiraz	South	226	200	88.5%	ELISA	[166]
					196	86.7%	RIBA	
					59	26.1%	RT-PCR	
Khosravi		Fars	South	101	87	86.1%	ELISA	[172]
Alipour	2011	Shiraz	South	1444	1132	78.4%	ELISA	[169]
Davoodian	2002	Bandar Abbas and Roodan	South	38	35	94.0%	ELISA	[85]
Zahedi	2011	Kerman	South-East	165	122	73.9%	ELISA	[165]
Sharifi-Mood	2000-2005	Zahedan	South-East	52	6	11.5%	ND	[162]
Alavi	2001-2003	Ahvaz	South-West	104	77	74.04%	ELISA	[171]
Saleh	2013	Khorramabad, Lorestan	West	103	23	22.3%	ELISA	[174]
Mohammadi	2007-2008	Lorestan	West	391	282	72.0%	ELISA	[163]

ND: Not defined; ELISA: Enzyme linked immunosorbent assay; RT-PCR: Reverse transcriptase polymerase chain reaction; RIBA: Recombinant immunoblot assay.

the older homeless population and homeless IDUs, especially those with a history of imprisonment[157,158]. The seroprevalence of HCV was reported to be 3.5% among the street children in Tehran city in 2008[160], while it was 1.0% in Isfahan city in 2005-2007[161].

The prevalence of HCV infection among homeless populations is higher than the other blood-borne infections, therefore, HCV infection is the main health problem among homeless population of Iran and implementation of HCV-controlling and educational programs are required to reduce HCV infection among this population[157,158,161].

HCV in human immunodeficiency virus-positive patients

Prevalence of HCV coinfection among human immunodeficiency virus (HIV) positive patients ranges from 11.5% to 94.0% in different regions of Iran[85,162] (Table 7[85,162-174]). This geographic variation in HCV/HIV coinfection reflects diversity of the risk factors, the types of exposure, and the epidemiology of these viruses in different regions of the country[163,164]. However, in all of these studies, intravenous drug use and a history of imprisonment were the most prevalent risk factors for HCV/HIV co-infection in Iran[164-169].

The prevalence of HCV coinfection is noticeably high among HIV-positive patients in Iran. The shared modes of transmission and the lack of an effective vaccine for HCV could explain this high prevalence[163-165,169,170]. In Iran, HCV and HIV are predominantly transmitted by injecting drug use[165,170,171]. Moreover, the rate of IDUs is increasing in Iran, which may boost the rate of HCV/HIV coinfection in the country[163].

HCV coinfection adversely affects HIV disease outcomes and leads to severe liver disorders, progression to cirrhosis and HCC, and subsequently lower survival of HIV infected patients[163-165]. HIV infection leads to higher rates of HCV persistence, increased risk of hepatotoxicity due to the extensive use of anti-retroviral drugs, and subsequently accelerated end stage liver disease[164,169-171]. Overall, one third of mortalities in HIV infected patients are related to liver diseases[163,164,170]. Therefore, HCV coinfection is considered a potential threat to HIV positive patients, and routine screening for HCV infection, as well as HCV treatment, seem to be necessary in all HIV-positive patients[164,165,169,172].

HCV IN IMMUNOLOGICAL DISORDERS

HCV in patients with mixed cryoglobulinemia

Mixed cryoglobulinemia is the most common immunological disorder reported in patients with chronic HCV infection[175-177]. The prevalence of HCV infection in patients with mixed cryoglobulinemia ranges from 40% to 90% worldwide[178]. Several studies have reported HCV infection as the etiological agent of mixed cryoglobulinemia[176,179,180]. Gharagozloo *et al*[181] reported an anti-HCV prevalence of 69% among patients with mixed cryoglobulinemia in Iran. In Owlia *et al*[182], 16% of patients (8/50) with HCV infection had cryoglobulins in central regions of Iran. However, this rate was relatively low in comparison with the high incidence of mixed cryoglobulinemia (19%-> 50%) among patients with chronic HCV infection.

HCV in patients with diabetes mellitus

Diabetes mellitus is one of the most prevalent metabolic disorders, and it affects 4.6%-10.0% of the Iranian population[183]. In 1994, a possible association between HCV infection and diabetes mellitus was first introduced[184]. Since then, many studies have demonstrated that HCV infection has a role in the activation of host innate immune responses and, *via* the TNF-α pathway, induces the destruction of insulin

signaling pathways and subsequently the development of insulin resistance[185]. In addition, immune-mediated pathogenesis or direct cytotoxic effects of HCV on pancreatic islet cells results in dysfunction of β cells and declines the insulin production[183,185-188]. Although HCV infects the pancreas, autoimmunity is not involved in the occurrence of diabetes[186].

Several studies have shown that the prevalence of HCV among diabetic patients is significantly higher than that in non-diabetic patients[187,189,190]. Interestingly, male gender, age over 40 years, and abnormal liver enzymes are associated with high prevalence of HCV infection among patients with diabetes mellitus[191]. Although there are several reports on the prevalence of HCV infection among patients with diabetes mellitus in Iran, the results show great heterogeneity. Aghamohammadzadeh *et al*[192] reported HCV seropositivity in 2.5% (10/400) of Iranian patients with diabetes mellitus in Tabriz. In addition, Alavian *et al*[193] showed an increased risk of diabetes mellitus among Iranian patients with chronic HCV infection in Tehran. While, Janbakhsh *et al*[194] reported no association between HCV infection and the occurrence of diabetes in Kermanshah. Metanat *et al*[195] found no association between HCV and diabetes in Zahedan, and Bahar *et al*[196] reported similar findings in Tehran.

According to the epidemiological data, patients with chronic HCV infection are at an increased risk for developing diabetes[191,197,198]. HCV infection is a risk factor for occurrence of diabetes, and diabetes will enhance the risk of liver fibrosis, cirrhosis, and finally progression to HCC[187]. Therefore, screening of all HCV positive patients for diabetes mellitus is recommended to reduce the adverse effects associated with diabetes on HCV infection, which may progress to liver fibrosis, cirrhosis, or even HCC.

The incidence of diabetes mellitus among HCV positive patients ranges from 23% to 62% in different parts of the world[183]. This incidence is 18.3% among Iranian HCV-infected patients, which is higher than that in the general population of Iran[183]. Compared to other parts of the world, the prevalence of diabetes mellitus among Iranian patients with HCV infection is low. Overall, there are no adequate studies in this field in Iran. Therefore, more surveys are recommended to clearly identify the frequency of diabetes mellitus among HCV-infected patients in Iran.

HCV in patients with autoimmune thyroid disorders

Autoimmune thyroid disorders (ATD), including Hashimoto's thyroiditis and Graves' disease, are the most prevalent endocrine problems worldwide[199,200]. Many investigators have investigated the possible association between chronic HCV infection and autoimmune thyroiditis. However, the exact role of HCV infection in the development of autoimmune thyroiditis remains unclear[201]. Investigations have suggested several mechanisms, including the following: (1) Non-autoimmune-mediated pathogenesis through direct cytopathic effect of HCV on thyrocytes, which results in destruction of thyroid follicular cells[201]; (2) Autoimmune-mediated pathogenesis due to the presence of homologous amino acid sequences between viral proteins and thyroidal proteins or molecular mimicry and over activation of autoreactive T-cells and B-cells during HCV infection, which results in production of anti-thyroid antibodies[200-202]; and (3) The adverse effects of IFN-therapy on thyroid gland through immune stimulatory and direct effects of IFN on the thyrocytes, which ultimately results in destructive thyroiditis[199,201,203]. Therefore, monitoring thyroid function is recommended during IFN-therapy in patients with HCV infection[201,204].

There are limited reports on the significance of HCV infection in patients with ATD in Iran. Ziaee *et al*[204] reported thyroid dysfunction in 10.3% of patients with chronic HCV infection in Tehran in 2002-2003, while, Rahimi *et al*[205] found no relationship between chronic HCV infection and autoimmune thyroiditis in Kermanshah in 2010. Similarly, Jadali *et al*[206,207] reported no relationship between HCV infection and Hashimoto's thyroiditis or Graves' disease in Tehran in 2005. Still, more studies are recommended to generate a clear epidemiological pattern of HCV infection among patients with thyroid disorders in Iran.

HCV in patients with lichen planus

Lichen planus (LP) is a chronic inflammatory disease of the skin and mucous membranes with unknown etiology[199,208,209]. Chronic HCV infection appears to have a role in the pathogenesis of LP through induction of host immune responses and immune dysregulation in susceptible patients[200,210,211]. This mechanism was confirmed by the presence of HCV-RNA and HCV-specific T lymphocytes in the skin and mucous membrane specimens of patients with LP[200,209]. Another possibility is the effect of IFN-therapy in the development of LP in patients with HCV infection[209]. However, HCV replicates in skin and mucous lesions of patients with LP, but no direct cytotoxic effect of HCV on skin and mucosa cells could be proposed in the development of LP[209]. The majority of patients with LP have not been infected with HCV[212]. In addition, the incidence of LP among patients with chronic HCV infection was estimated about 5% (1%-6%)[199,209]. Therefore, it seems that HCV contributes to the development of LP, with some unknown underlying factors also involved in this process[210].

According to the epidemiological data, the prevalence of HCV among LP patients varies considerably from 4% to 62% in different parts of the world, where this prevalence is higher in HCV endemic countries[209,210]. There are limited reports on the prevalence of HCV among patients with LP in Iran. Rabiei *et al*[213] reported high prevalence of oral lichen planus (OLP) in HCV-infected patients (4.7%) compared

to the general population (0.5%-2.0%) and suggested an association between HCV infection and OLP in Gilan in 2002. Similary, Khatibi *et al*[214] reported a higher prevalence of OLP in HCV-infected patients (4%) than the general population in Tehran. In contrast, Rahnama *et al*[215] reported no association between LP and HCV in Kerman in 2005. Similarly, Taghavi Zenouz *et al*[216] found no relationship between LP and HCV in Tabriz in 2009, and Ansar *et al*[208] reported a similar result in Hamedan province in 2011. Overall, Petti *et al*[212] reported a weak association between HCV and OLP in Iranian population. Further investigations are needed to clearly identify the association between HCV and LP in Iran.

HCV IN MALIGNANCY

HCV in patients with B-cell non-Hodgkin's lymphoma

HCV is not only primarily hepatotropic, but it can also affect lymphatic systems and lead to B cell lympho-proliferative disorders such as non-Hodgkin's lymphoma (NHL)[217]. Few studies have evaluated the relationship between HCV seropositivity and the incidence of NHL in Iran. Aledavood *et al*[218] reported low prevalence of HCV infection among patients with NHL (0.7%) compared to the general population (0.5%-1%) and found no relationship between HCV infection and NHL in Northeast of Iran in 2014. In contrast, Rezaeian *et al*[219] reported high prevalence of HCV in patients with NHL (15.7%) compared to the control group (0%) and suggested an association between HCV infection and NHL. Similarly, Rastin *et al*[217] found a HCV prevalence of 7.4% among patients with NHL in Mashhad city. NHL is prevalent worldwide and is the eighth and 11th most common cancer in males and females, respectively[220]. Although the exact risk factor for NHL has not yet been determined, it seems that HCV infection has a role in the pathogenesis of this lymphoproliferative disorder[178].

According to the results of a meta-analysis study, the global prevalence of HCV infection in NHL patients is approximately 15%, which is higher than the prevalence of HCV in general population (1.5%), suggesting a possible role of HCV infection in the development of NHL[221]. Although the role of other factors, such as genetic and environmental factors, should also be considered in the pathogenesis of NHL malignancy[217,221].

HCV in patients with HCC

HCC is the fifth most common malignancy and the second most fatal cancer, with approximately 600000 deaths annually worldwide[222]. HBV and HCV infections account for 50% and 25% of global HCC cases, respectively. However, HCV infection is the most predominant cause of HCC in Japan and the United States[222]. Iran is considered a low endemic area for HCC, with less than five cases per 100000 persons annually[26,223]. Kerman province, located in Southeast of Iran, has a higher incidence of HCC compared to other provinces. This may be due to higher frequency of HBV and HCV infections in this part of the country[224].

In Hajiani *et al*[225]'s study, the seroprevalence of HBV and HCV infections among patients with HCC in southern Iran were 52.1% and 8.5%, respectively. They pointed out that the prevalence of HCV infection among HCC patients may be underestimated due to the potential contribution of occult HCV infection in the development of HCC. Therefore, the prevalence of occult HCV infection among patients with HCC should be investigated in future surveys. Ansari *et al*[135] found a very low incidence of HCC (0.6%) among thalassemia patients with HCV infection due to the anti-HCV treatment in this group of patients. In Iran, HCV is the second most common cause of HCC after HBV infection[26,223]. However, it is predicted that chronic HCV infection will replace HBV infection as the main cause of HCC in the future[26].

DISTRIBUTION OF HCV GENOTYPES IN IRAN

HCV genotypes differ in their nucleotide sequence and biological properties, such as pathogenicity, infectivity, antigenicity, response to antiviral therapy, mode of transmission, as well as geographical distribution and age-distribution[226,227]. Distribution of HCV genotypes is variable in different regions of Iran (Table 8[101,102,128,131,228-251]). Subtypes 1a is more prevalent in southern and northern Iran, 3a is more prevalent in northern and central Iran, 1b is more prevalent in southern and western Iran, and genotype 2 is more prevalent in western regions of Iran[4,226,228]. Overall, the most frequent genotype in Iran is 1a, followed by 3a and 1b[4].

Distribution of HCV genotypes in Iran is different from other Middle Eastern countries with predominant genotype 4, but it is similar to the pattern seen in North America, with predominant genotypes 1, 2, and 3[4]. Genotype 2 is generally uncommon in Iran, therefore, the genotypic pattern differs from the United States, Europe, and Asia but is similar to Pakistan and India, where genotype 2 is very rare[226,229]. Genotype 4 is uncommon in Iran and only seen in special patient groups[226]. A similar pattern regarding genotype 4 is seen in Europe, the United States, and India. However, due to changes in immigration patterns, the prevalence of genotype 4 is increasing in western countries in recent years (Table 9)[4,229,230]. Overall, the worldwide distribution of HCV genotypes shows that the genotypes 1, 2, and 3 have a global prevalence, while genotypes 4, 5, and 6 have a restricted prevalence[4,226,229,231].

Different HCV genotypes may be associated with particular patient groups. Therefore, the genotypic patterns can be used to trace the routes of transmission[4]. Genotype 1 is more prevalent among thalassemia, hemophilia, hemodialysis, and solid organ

Table 8 Distribution of hepatitis C virus genotypes among hepatitis C virus -infected patients in Iran *n* (%)

Study group	City or province	Location	Year of study	Sample size	Genotype 1	Genotype 2	Genotype 3	Genotypes 4 and 5	Mixed genotype	Non typable	Method	Author	Ref.
Blood donors	Ahvaz	South-West	2007-2008	45	1a: 24 (53.3)		3a: 21 (46.7)				RFLP	Farshadpour	[233]
Blood donors	Tehran	North-Center	2006-2008	103	1a: 53 (51.5) 1b: 4 (3.9)		3a: 39 (37.9)			7 (6.8)	Type-specific primers	Sharifi	[234]
General population	Iran	Iran	2000-2005	116	1a: 71 (61.2) 1b: 16 (13.8)		3a: 29 (25.0)				RFLP	Amini	[235]
General population	Iran	Iran	2004-2007	206	1a: 53 (25.73) 1b: 36 (17.47)	2: 4 (1.95)	3a: 96 (46.60)		11 (5.34)	6 (2.91)	PCR kit	Hajia	[236]
General population	Isfahan	Center	2007-2009	97	1a: 29 (29.5) 1b: 5 (5.1)	2: 2 (2.0)	3a: 59 (61.2)		2 (2.0)		PCR based genotyping kit	Zarkesh-Esfahani	[237]
General population	Zanjan	West	2007-2013	ND	1a: 22.05% 1b: 25.73%	2: 5.14%	3a: 38.26%	4: 4.41%		4.41%	LiPA	Esmaeilzadeh	[238]
General population	Yazd	Center	2010-2013	191	1a: 74 (38.7) 1b: 13 (6.8)	2: 3 (1.6)	3: 96 (50.3)		5 (2.6)		PCR based genotyping kit	Hadinedoushan	[239]
General population	Mashhad	North-East	2009-2010	382	1a: 147 (39.2) 1b: 41(10.9)	2a: 9 (2.4)	3a: 150 (40.0)	5: 13(3.4)			Genotype specific primers	Vossughinia	[240]
General population	Tehran	North-Center	2007	2231	1a: 886 (39.7) 1b: 271 (12.1)		3a: 613 (27.5)		33 (1.6)	401 (18.0)	Genotype specific primers	Keyvani	[241]
General population	Golestan	North	2010	77	1a: 15 (19.5) 1b: 15(19.5)	2a: 2 (2.6)	3a: 12 (15.6) 3b: 19 (24.7)	4: 6 (7.8)	8 (6.5)		Genotype specific primers	Moradi	[242]
General population	Ahvaz	South-West	2009	80	1a: 43 (53.8)		3a: 37 (46.2)				RFLP	Hamidi-Fard	[243]
Thalassemia	Mazandaran	North	2009-2011	34	1a: 13 (38.24) 1b: 1 (2.94)		3a: 15 (44.12)		4 (11.76)	1 (2.94)	Type-specific primer	Rafiei	[244]
Thalassemia	Mazandaran and Guilan	North	2010	28	1a: 9 (32.1) 1b: 1 (3.6)		3a: 18 (64.3)				RFLP	Ghane	[245]
Thalassemia	Fars	South	2009-2012	38	1: 17 (44.7)		3: 6 (15.8)			15 (39.5)	Real-time PCR	Jamalidoust	[231]
Haemophilia	Mazandaran	North	2009-2011	33	1a: 7 (21.21)		3a: 25 (75.76)			1 (3.03)	Type-specific primer	Rafiei	[244]
Haemophilia	Fars	South	2009-2012	8	1: 5 (62.5)		3: 1 (12.5)			2 (25.0)	Real-time PCR	Jamalidoust	[231]
Haemophilia	Ahvaz	South-West	2008-2009	42	1a: 26 (61.9) 1b: 11 (26.1)		3a: 5 (11.9)				Genotype specific primers	Assarehzadegan	[131]
Haemophilia	Markazi	West-Center	2004	22	1: 6 (27.3) 1a: 3 (13.6) 1b: 2 (9.1)	2: 1 (4.54)	3a: 4 (18.2)		6 (27.3)		LiPA	Samimi-Rad	[128]
IDUs	Mazandaran	North	2009-2011	37	1a: 11 (29.73) 1b: 10 (27.03)		3a: 5 (13.51)		11 (29.73)		Type-specific primer	Rafiei	[244]
IDUs	Tehran	North-Center	2008-2009	36	1a: 9 (25) 1b: 6 (16.7)		3a: 21 (58.3)				Type-specific primers	Ranjbar Kermani	[246]
IDUs	Fars	South	2009-2012	550	1: 283 (51.5)		3: 192 (34.9)		8 (12.2)	67 (12.2)	Real-time PCR	Jamalidoust	[231]
IDUs	Tehran	North-Center	2008-2009	83	1a: 35 (42)		3a: 48 (58.0)				Sequencing	Samimi-Rad	[247]
Haemodialysis	Mazandaran	North	2009-2011	31	1a: 6 (19.36)		3a: 24 (77.42)		1 (3.22)		Type-specific primer	Rafiei	[244]
Haemodialysis	Markazi	West-Center	2005	8	1a: 4 (50) 1b: 1 (12.5)		3a: 1 (12.5)	4: 2 (25)			LiPA	Samimi-Rad	[102]
Haemodialysis	Fars	South	2009-2012	6	1: 4 (66.7)			4: 1(16.7)		1 (16.7)	Real-time PCR	Jamalidoust	[231]

Haemodialysis	East Azerbaijan	North-West	2006	55	1a: 42 (76.4) 1b: 3 (5.5)	3a: 3 (5.5)		1 (1.8)	4 (10.9)	Type-specific primer	somi	[248]
Haemodialysis	Gilan	North	2008	32	1a: 19 (59.4)	3a: 13 (40.6)				Genotype-specific primers	Joukar	[101]
Haemodialysis	Tehran	North-Center	2004	66	1a: 19 (28.8) 1b: 12 (18.2)	3a: 20 (30.3) 3b: 2 (3.0)	4:11(16.7)	2 (3.0)		RFLP	Hosseini-Moghaddam	[249]
HIV/HCV co-infection	Shiraz	South	2004-2005	50	1a: 20 (40) 1b: 13 (26)	3a: 17 (34.0)				RFLP	Davarpanah	[250]
Occult HCV infected patients	Tehran	North-Center	2007-2010	7	1a: 2 (29) 1b: 3 (43)	3a: 2 (29.0)				RFLP	Bokharaei-Salim	[251]

ND: Not defined.

recipient patients[231]. Subtype 1b is prevalent in individuals with a history of hospitalization, surgery, blood transfusion, and alcohol consumption[226]. Subtype 1a is frequently found in infection by blood and blood products[228]. High frequency of genotypes 3a and 1a are seen among IDUs in Iran[228], which is similar to the genotypic pattern among IDUs in Europe and the United States[226]. Genotype 4 is found in patients undergoing hemodialysis and piercing[226,228]. This might be due to communication by dialysis during the Hajj ceremony in Saudi Arabia[4]. The mixed infection with two or more genotypes is more common in patients with hemophilia and thalassemia and may lead to chronic infection, more severe disease, re-infection, and poor response to therapy[2,4].

There has been a shift in the distribution pattern of HCV genotypes over time[4,6,232]. Genotype 1a is the most prevalent genotype in Iran, but in recent years, an increase in the frequency of 3a and a decrease in 1a and 1b have been reported among HCV-infected patients in Iran. Genotype 1 with subtypes 1a and 1b are more prevalent in older patients and genotype 3a in younger patients and IDUs[4,228,232]. Therefore, it seems that injection drug use has contributed to the majority of new HCV infections in Iran[4,232].

Distribution of HCV genotypes is variable in different groups and geographic regions of Iran. This genotypic variability reflects differences in the routes of transmission, population and socioeconomic factors, and the presence of risk factors in the society. Thus, some genotypes are more frequent in certain regions or groups of patients[4,232]. Studies on the molecular epidemiology of HCV in Iran are needed to reveal the current genotypic pattern of HCV infection in the country[228], which can predict the dose, duration, and type of treatment as well as clinical outcome of the infection[2,228-231].

OCCULT HCV INFECTION IN IRAN

Occult HCV infection is described by the absence of detectable HCV-RNA and anti-HCV antibodies in serum or plasma with elevated liver enzymes or by the presence of anti-HCV antibodies but undetectable levels of HCV-RNA in serum or plasma with normal levels of liver enzymes[252-254]. In both cases, HCV-RNA is detectable in 100% of liver biopsy, up to 70% of peripheral blood mononuclear cells (PBMCs) specimens, and in nearly 60% of ultracentrifugated serum samples of infected patients[255]. Occult HCV can persist and replicate in hepatocytes and lymphoid cells for a long time even after an apparently spontaneous eradication or therapy-induced resolution of HCV infection[256]. In this condition, low copy numbers of HCV RNA are present in serum while it cannot be detected by conventional RT-PCR assays but remains potentially infectious[253,254].

Distribution of occult HCV infection has been reported all around the world, and it seems that all genotypes are involved in this infection[253]. A few studies are available regarding the prevalence of occult HCV in Iran. Bokharaei-Salim *et al*[251] found occult HCV in 10% (7/69) of patients with cryptogenic liver disease in Iran, while 43%, 29%, and 29% of these patients had genotypes 1b, 1a and 3a, respectively. Keyvani *et al*[257] described 8.9% occult HCV infection with genotypes 3a (50%) and 1b (50%) in patients with cryptogenic cirrhosis in Iran. Farahani *et al*[258] found 1.9% occult HCV infection with genotype 1a in patients with lymphoproliferative disorders in Iran. Makvandi *et al*[259] reported 32% occult HCV infection in patients with abnormal levels of alanine aminotransferase in Ahvaz city. Rezaee Zavareh *et al*[260] reported the absence of HCV-RNA in PBMC samples of 53 patients with autoimmune hepatitis in Iran. Ramezani *et al*[261], reported the absence of occult HCV

Table 9 Global distribution of hepatitis C virus genotypes[4,229,230]

Region/country	Predominant genotype/subtype	Uncommon genotype/subtype
Latin America		
Peru	1a	2
Chile and Colombia	1b	2, 1a
Brazil	1b, 1a, 3	4, 2
Argentina	1b, 2, 1a	4
North America		
United States	1a, 1b, 2	4, 3
Canada	1a, 3, 1b	4
Central Europe		
Albania	1b, 2, 4	1a, 3
Bosnia and Herzegovina, Czech Republic and Croatia	1b, 3	4, 2, 1a
Hungary	1b, 1a	2, 4
Romania	1b	3, 4
Western Europe		
Switzerland, Belgium, Germany, Spain and France	1b, 3, 1a	5, 2, 4
Italy	1b, 2	5, 3, 4
United Kingdom and Denmark	3, 1a	2
Eastern Europe		
Russia, Latvia, Lithuania and Estonia	1b, 3	1a, 2
Central Africa	4	2
South Africa	5	2
West Africa		
Guinea-Bissau, Ghana and Burkina Faso	2	1
East Africa		
Ethiopia	4, 2	1
North Africa		
Tunisia, Morocco, Algeria	1b, 2	4
Middle East		
Saudi Arabia, Bahrain, Yemen, Kuwait, Qatar, Iraq and Egypt	4	1, 3, 2
Jordan	1a, 1b, 4	-
Iran	1a, 3a, 1b	4, 2
Turkey	1b	4, 2, 3, 1a
Asia Pacific		
Japan and Korea	1b, 2	1a
Asia, Central		
Uzbekistan, Tajikistan, Turkmenistan and Georgia	1b	1a
East Asia		
China, Taiwan	1b, 2	1a, 3, 6
South East Asia		
Laos	6	1
Philippines	1a, 2	6, 4
Thailand	3	2
Myanmar	6	2
Malaysia	3	4
South Asia		
Pakistan and India	3	1b, 2, 4
Australasia		
Australia and New Zealand	3, 1a, 1b	4, 2

infection in 30 hemodialysis patients in Tehran.

Occult HCV infection has also been found in apparently healthy populations[253,255]. The possible presence of occult HCV infection in the general population or blood donors poses a real concern about undetectable transmission of HCV[255,262]. In a recent study in Italy, the prevalence of occult HCV infection was higher than the frequency of anti-HCV seropositivity in the general population[262]. Therefore, the prevalence of HCV infection may be underestimated in the society[253,255], and the risk of HCV transmission through blood donation may be higher than predicted. Although screening of blood reduces the risk of HCV transmission by blood transfusion, transmission of occult HCV cannot be prevented in this way[253,255].

Currently, the prevalence of occult HCV infection in the general population of Iran and even blood donors is unknown. Therefore, further studies on the prevalence and significance of occult HCV in different cities are needed to identify the real burden of this infection in the country and subsequently in healthy subjects, especially among blood donors, to prevent the most of unknown transmission of HCV.

CONCLUSION

HCV infects large proportion of the high-risk populations in almost all regions of Iran and has a role in occurrence of different immunological disorders and even malignancies. The distribution patterns of HCV infection are related to different status of public health and the presence of risk factors in the society. Available estimates emphasize that injecting drug use is the most important risk factor for HCV infection in Iran and due to the growth in the number of injecting drug users, the prevalence of HCV infection is growing in the country. In addition, it seems that injection drug use has contributed to the occurrence of the majority of new HCV infections in Iran. Even the recent changes in the distribution pattern of HCV genotypes in Iranian patients confirm this issue. In fact, the predominance of risk factors for transmission of HCV has changed over time, from blood transfusion to intravenous drug use. The possible presence of occult HCV infection among the apparently healthy general population or blood donors proposes a real concern about undetectable transmission of HCV. Therefore, it seems that the prevalence of HCV infection will increase in near future not only among high-risk groups but even in the general population and blood donors of Iran. However, by breaking the cycle of infection among drug users, the rate of HCV infection will decrease. To approach this goal, efforts to screen, prevent, and treat HCV infection as well as reduce the high-risk behaviors are required.

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