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REVIEW ARTICLE

Hepatitis C Infection in the General Population of Iran: A Systematic Review

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Background and Aims: **There is no overall estimate of hepatitis C infection (HCV) in Iran. We reviewed all of the published and unpublished evidence related to HCV infection in Iran in order to accurately estimate the prevalence of HCV infection in the Iranian general population to inform future health system programs.**

Methods: **In this systematic review, all papers, medical congresses, HCV-related reports, projects of Iranian research centers and medical universities, reports from the Deputy for Health Affairs (published or unpublished), and online theses about HCV in Iran were included. We selected descriptive and analytic cross-sectional studies and surveys related to the prevalence of HCV infection in the Iranian general population between 2001 and 2008 that have sufficiently declared objectives, proper sampling methods with identical and valid measurement instruments for all study subjects and proper analysis methods regarding sampling design and demographic adjustments. We used a survey data analysis method to estimate the national prevalence rate.**

Results: **From the 6,431 studies we investigated, eight eligible studies reported a prevalence of HCV infection in the general population. They were from six (out of 30) provinces, in which about 43 percent of the country's population lives. We calculated that the HCV infection prevalence rate in Iran is 0.16% (95% confidence interval [CI]: 0%-0.59%).**

Conclusions: **In comparison with similar studies, the prevalence of HCV infection in Iran is low. This might be a result of having prevention programs for high-risk groups and strict blood screening programs.**

Keywords: **Hepatitis C, Iran, Prevalence, Epidemiology**

Introduction

Hepatitis C virus (HCV) infection is a major global public health problem in both developed and developing countries [1]. HCV infection is transmitted mainly by exposure to infected blood or blood products, infected medical equipment despite strict hygienic control, intravenous drug abuse, hemodialysis, and organ transplantation [2, 3]. There are some studies on the prevalence of HCV infection in the Iranian population that have focused specifically on healthy blood donors. The first paper in this line of literature was published in 1994 and found the prevalence of HCV infection to be 0.3% in blood donors [2]. In previous studies, the prevalence of HCV infection

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was reported to be between 0.08% and 1.3% of the Iranian general population and blood donors in different provinces [3-6]. According to the Iranian national census of 2006, the national population of Iran was 70,495,782 persons [7].

In 2003, it was estimated that HCV infection affected nearly 170 million people worldwide [8]. The rate of occurrence in some regions or among high-risk groups such as injecting drug users, Hemophilia and thalassemia patients, and patients undergoing hemodialysis may be as high as 30%-90% [9]. Epidemiologic evidence of HCV is one of the main evidences for strategic prevention of chronic liver diseases.

HCV infection is detected by some laboratory methods such as enzyme-linked immunosorbant assay (ELISA), recombinant immunoblot assay (RIBA), and polymerase chain reaction (PCR). Generally ELISA is used as a screening tool, RIBA is used as a complementary test, and PCR is used as a confirmatory test. HCV antibody detection with ELISA has a low specificity and positive predictive value for low-risk groups such as blood donors and the general population [10]. In one study in China, with a single ELISA test as the HCV detection method, the false negative rate was nearly 17% in HCV infectors. After adding PCR to ELISA for HCV detection, false positive results decreased [11]. Assessment of predicted rate for infected patients, diagnosis and treatment of high-risk groups in the community could be achieved by most effective and preventive programs in reducing the rate of HCV infection. This, or any other effective program, needs more accurate estimates of the prevalence of HCV infection in the country.

In Iran, we do not have an overall estimate of HCV infection, and the studies that have been done on HCV prevalence are restricted to specific geographic locations or provinces.

In the present systematic review, we reviewed the papers on HCV infection in Iran in order to accurately estimate the HCV infection prevalence rate in Iran in order to help promote HCV prevention programs.

Materials and Methods

We estimated the prevalence of HCV in the Iranian general population with a comprehensive systematic review of the literature and evidence followed by integrating the data and an analysis of the findings.

Study question

Our study population was the Iranian general population, and the outcome of interest was the presence of positive HCV antibody in blood samples of the study population, based on any of the blood tests such as ELISA or RIBA/PCR even if other laboratory tests are not identified clearly, from April 2001 to March 2008.

Search strategy

For electronic and hand searching we used "Hepatitis C", "HCV," and "Iran" (or the names of its provinces) as key words for titles and/or abstracts in a MeSH word search. We also used different text words (specifically in searching national databases) to increase the sensitivity of the search.

Electronic databases

We searched 15 electronic databases of the health and biological sciences including Google Scholar, ISI, Scopus, EMBASE, Medline, WHO, CINAHL, DOAJ, CABI, High-Wire Press, EBM Review, EMR medex, Cochrane, NLM Gateway, and DARE. Furthermore, four Iranian databases on the medical and life sciences literature were used including Iran Medex, SID, Magiran and IranDoc. Hence, the study covered all registered and certified life sciences and medical journals at the national level.

Gray literature search

In a gray literature search, we found 243 national, regional, and international Iranian medical science congresses in the study time period. We selected and hand searched 67 out of 243 relevant congress` abstract books by two independent reviewers. We also searched the research projects of 29 out of 40 Iranian universities of medical sciences from their websites. We contacted the Center for Disease Control (CDC) of the Iranian Ministry of Health and the Iranian Blood Transfusion Organization (IBTO) for searching national reports from the study time period. Medical students' theses were also evaluated by two independent reviewers from the Iranian center for scientific documents and records (IranDoc). Finally, we consulted eight expert HCV researchers in Iran and searched their personal archives for additional citations. Forward and backward citations of searched items were also performed.

Critical appraisal and selection of studies

Two independent reviewers reviewed all citations thoroughly and checked for eligibility criteria to include the studies in the analysis. The inclusion criteria were all cross-sectional studies that specified temporal and geographic characteristics of the study; sufficiently declared objectives; and that used a valid

sampling method that allowed for a generalization of the findings to the target population, valid measurement instruments for all study subjects, and appropriate analytic methods for the given sampling design and demographic characteristics. We revised the criteria developed by Sharifi *et al.* for this purpose [12].

Data extraction

After evaluating studies on these criteria, we extracted the findings of the included studies to Excel spreadsheets. The extracted data were year of the study, first author, province and district of the study, sample population, sampling method, sample size, HCV Antibody detection method, HCV Antibody kit name, mean age and standard error (SE) of subjects, percentage of male subjects, and HCV point prevalence in study subjects and/or in males/females and its SE. If there were other parameters reported other than SE, such as standard deviation, confidence interval, and/or P.value, the proper modifications were performed to calculate SE.

Statistical analysis

We analyzed the extracted data to estimate the point prevalence of HCV infection and its 95% confidence interval (CI) and used a Cochrane Q-test with a significance level of < 0.1 for checking the statistical heterogeneity of the results. We used a meta-analysis method with the "meta" command using fix/random model based on the results of the heterogeneity test. It seems that the meta-analysis method would not have been a suitable method to achieve the objectives of this systematic review because the weighting system of this method only considers sample size and not the size of the provincial population. We used a survey data analysis method to calculate the estimate of the nationwide prevalence rate considering the weight of each province as the ratio of the provincial population to the sample size(s), where the population of each province was retrieved from the Iranian national census at 2006 [7].

In provinces with more than one prevalnce study (Tehran and Sistan-va-Baluchestan), the provincial prevalence was calculated by a meta-analysis of the studies, and the total sample size was determined by adding all study sample sizes. The analysis was performed with STATA 9.1 software (STATA Corp. LP). The results were shown in geographic maps using Arc View 3.2a software (ESRI Inc. NY).

Results

Search results

After review of studies, we found 190 related studies about HCV prevalence in Iran in literature review [13-192] from 264 studies that were found in electronic databases (Fig. 1). We found no additional unpublished findings on the HCV infection rate in

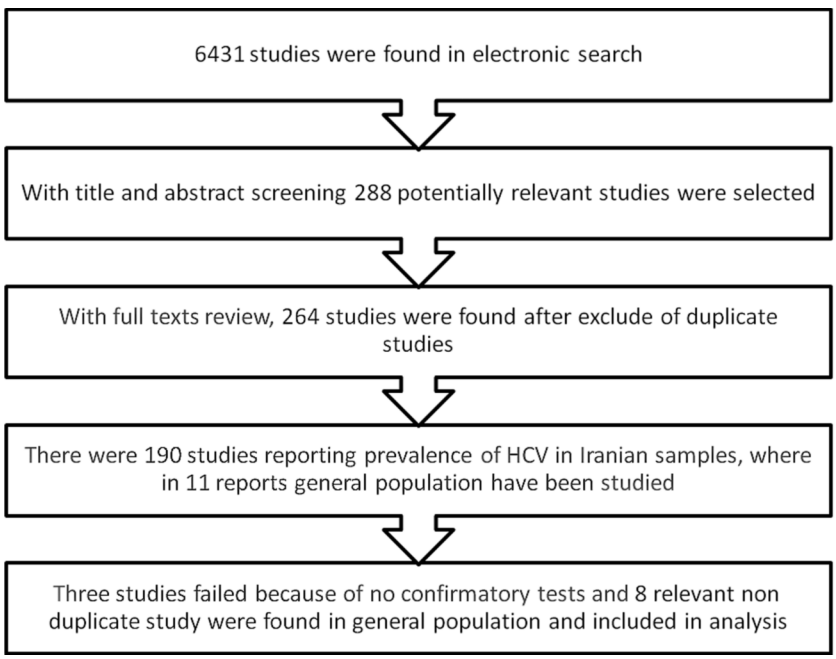

Figure 1. Diagram of the systematic review and searches for HCV infection prevalence in I.R. Iran.

the general population from Iranian medical congresses and reports.

Studies

After excluding duplicate and overlapping reports to avoid double counting, we finally selected eleven studies with subjects in the general population. Out of these, two studies were on the Sistan-va-Baluchestan province [98, 113], and three studies were on the Tehran [49, 96, 185] province. From East Azarbaijan [81], Kermanshah [93], Chaharmahal-va-Bakhtiari [30], Khuzestan [35], Guilan [3], and Golestan [25], one study from each province was included in our analysis.

HCV infection prevalence

The prevalence rate varied from 0% in the Khuzestan and Tehran provinces [35, 49] to 1.3% in the Guilan province [3]. Reported percentages were heterogeneous and statistically significant (Test for heterogeneity: Q= 1607.73, df = 10, P < 0.001) (Fig. 2).

The overall estimate of the HCV prevalence rate in Iran according to data from eleven studies from eight provinces with an ELISA detection test (For HCV-antibody) was 4.45% (95%CI: 1.29%-7.61%). In three studies from Chaharmahal-va-Bakhtiari, East Azarbaijan, and Tehran [96], confirmatory tests were not used; therefore, the studies were excluded from the final analysis. Prevalence of HCV in Iran with Survey Data analysis according to the information from eight studies from six provinces with RIBA/PCR for HCV infection was %0.16 (95%CI: 0%-0.59%) (Fig. 3).

Discussion

The present study was designed to estimate the HCV infection prevalence rate in the Iranian general population according to available data from literature collected from different provinces by Iranian medical researchers. The prevalence of HCV in Iran with RIBA/PCR for HCV infection was 0.16%.

In our study, the prevalence of HCV infection was evaluated in only eight provinces. These provinces were among the most populous ones in Iran. The total population of these provinces was 30,468,756, making up 43.2% of the country's population. Despite the lack of data for the country as a whole, it seems that the overall estimate in these provinces represents a suitable estimate of the HCV prevalence for the whole country.

The highest HCV infection rate in Iranian general population was reported from one study on the residents of a Guilan nursing home [3]. This rate might be due to the lower level of health in this sample. In two studies from Khuzestan [35] and Tehran [49], the HCV infection rate was reported to zero. These low rates could have been due to the study design or the type of sampling method and a small study population. HCV infection rates in provinces that border countries around Iran were significantly higher than the rates in the central regions of our country (Table 1). Some factors such

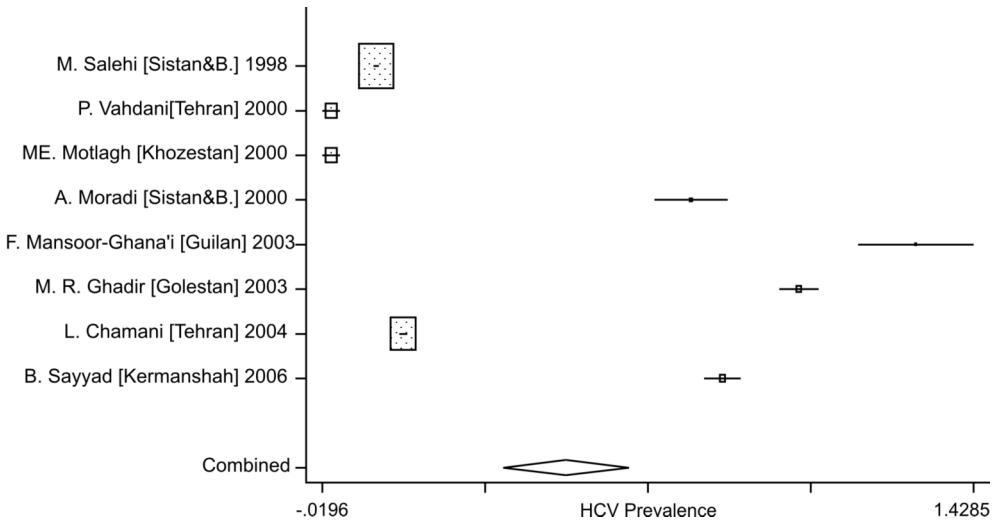

Figure 2. Forest plot of studies about HCV infection prevalence in I.R. Iran.

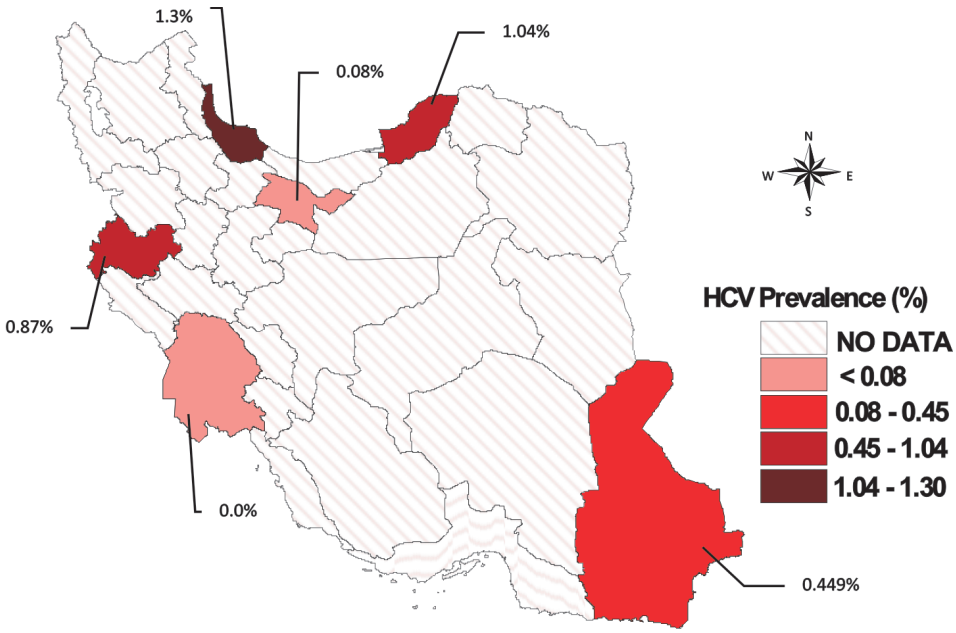

Figure 3. Prevalence of HCV in different provinces of Iran according to a RIBA/PCR test.

Table 1. HCV infection rate in several provinces of Iran.

Country region	Author/Year	Province	Neighbors	Kit	Sample size	Prevalence (%)	Reference
North	Ghanieie (2007)	Guilan	Azarbaijan (8.7%)	PCR	383	1.3	3
	Ghadir M (2006)	Golestan		RIBA	2123	1	25
West	Sayad B (2008)	Kermanshah	Turkey (2.4%)	PCR	1721	0.87	93
Southeast	Salehi M (2001)	Sistan va Baluchestan	Pakistan (3%)	WB*	919	0.1	98
	Moradi M (2007)	Sistan va Baluchestan		ELISA	365	0.8	113
Center	Vahdani P (2006)	Tehran	None	RIBA	102	0 £	49
	Chamani L (2007)	Tehran		ND	1249	0.16	190
Southwest	Motlagh (2001)	Kuzestan	Kuwait (0.8)	RIBA	80	0 §	35

*: western blot £: street children §: pregnant women

as more contact with infected patients and a higher prevalence of HCV in our neighbors may explain the probable cause of the different prevalence of these provinces.

The HCV infection rate in Iranian general population is lower in comparison with other countries in our region (Eastern Mediterranean Region) and even many other countries like China, Europe, and the USA [193-202] (Table 2).

One of the causes of the notable difference in the HCV prevalence rate might be due to the handling of HCV prevention programs by some countries [203, 204]. Preventive strategies in countries are based on health policy. Iranian prevention strategy for controlling the hepatitis C infection rate by harm reduction started 10 years ago. This strategy was accepted by the high-level officials of the government. More attention to high-risk groups to detect infected patients and screen and treat them was the fundamental basis of any program that was created with this strategy [205].

HCV prevention programs must be designed to control the risk factors that contribute to the transmission of HCV infection. Blood transfusion is one of the transmission routes of HCV infection. In developed countries, the residual risk for HCV infection through blood transfusion is lower and the current risk estimates per million donations are approximately 0.52 in the USA [206], 0.7 in Canada [207], and 0.1–2.33 in different European countries [208-210], In some developed countries, due to defects in the collection of samples from non-remunerated blood donors, lack of trained professionals, and a poor supply of instruments and laboratory equipment for suitable blood transfusion, HCV transmission occurs more than in developing countries [211]. In some studies, blood donors were selected as the general population. These samples are not actually representative of the general population and may have caused an underestimate of HCV infection in these studies [195]. The prevalence rate of HCV in donor populations in some developing countries ranges between 1% and 7% [212-215]. A high prevalence of 17% was reported in Egypt [216].

In Iran, we started a blood donor screening program in all Iranian blood transfusion centers in 1996. Some studies have shown that the HCV infection rate was significantly lower than before blood screening [29]. The screening process and the elimination of high-risk donors are among the main causes of improvement in blood transfusion services in Iran [154, 192]. The strict program of HCV infection screening prior to transfusion is one possible explanation for lower the prevalence of HCV infection rate in our country in comparison with other developing countries [217]. Some studies have reported that HCV infection has specific epidemiological characteristics in hemodialysis patients [218-221], thalassemia patients [217], hemophilic patients [88, 222], and intravenous drug abusers (IDUS) [82]. These patients are considered at-risk populations and are the primary source of

Table 2. HCV infection rate in several papers from the literature.

Author/Year	Country/region	Kit	Prevalence	Reference
Syed Asad Ali (2009)	Pakistan/EMRO	ND	3% (blood and non blood donors)	196
Sandesh K (2006)	India/EMRO	ND	0.33% (Blood donors)	197
Ameen. R (2005)	Kuwait/EMRO	ELISA	0.8% (Blood donors)	194
Daw. MA (2002)	Libya/EMRO	ELISA	1.6% (general population)	195
Erden S (2003)	Turkey/EMRO	-	2.4% (hospital based)	198
Lehman EM (2009)	Egypt/EMRO	-	13.9% (healthy populations)	199
Xia X (2008)	China/Asia	-	2.2% (general population)	200
Stvilia K (2006)	Georgia/Europe	RIBA	6.7% (general population)	201
Armstrong GL (2006)	USA/America	-	1.8% (Nationally representative household survey)	202
Galetski (1999)	Azarbaijan (Europe)	ND	8.7%	203

EMRO: Eastern Mediterranean Regional Office; ND: non determined; ELISA: enzyme-linked immunosorbent assay; RIBA: recombinant immunoblot assay.

HCV infection and can transmit HCV infection to other people as well. Some Iranian health programs have focused on screening transfused blood that is used for thalassemia and hemophilic patients and carefully controlling IDUS to help maintain and even decrease the HCV infection rate in the lower range [205, 223].

Fortunately, until now, Iranian prevention programs have focused on these special groups. We will control the HCV infection rate in the Iranian general population if we prevent the expansion of HCV infection from high-risk groups to the larger community. We will discuss this issue in our next systematic review, which will focus on special groups such as hemophiliacs, IDUSs, thalassemics, and patients who undergo hemodialysis.

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