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Prevalence of Hepatitis E in Iran: A Systematic Review of the Literature

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ABSTRACT

Introduction: Hepatitis E infection is caused by the hepatitis E virus (HEV) and is a self-limiting disease with moderate-to-high prevalence in various regions. Considering that HEV is endemic in Iran, the present study aimed to systematically review the prevalence of HEV in Iran.

Methods: This systematic review was performed in May 2016 to investigate the prevalence of Hepatitis E infection in Iran via searching in databases such as PubMed, Scopus, and IranMedex using the following approach: (((Hepatitis E OR HEV)) AND (epidemiology OR frequency OR prevalence)) AND Iran. After collecting the proper documents, the required data were extracted and described.

Result: In total, 24 relevant articles with 12,555 study populations were collected in this study. The results of the review indicated that the prevalence of HEV is relatively high in the Iranian population. In the reviewed literature, the prevalence of HEV varied from 2.3% to more than 40%.

Conclusion: According to the results, the prevalence of HEV in Iran is similar to the rate reported in the other developing countries. Therefore, it is recommended that routine tests be conducted for the diagnosis of hepatitis E, especially in the suspected cases of acute non-A, non-B, and non-C hepatitis.

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Introduction

Hepatitis E is a self-limiting disease caused by the hepatitis E virus (HEV) (1,2). HEV is a single-stranded, uncoated RNA virus and the only member of the hepevirus species from the Hepeviridae family (3,4).

Similar to the hepatitis A virus (HAV), HEV (previously known as non-A or non-B hepatitis) is transmitted through water and feces (2). In this regard, water is considered to be a more important route for HEV transmission than food (2,3,5). According to the literature, HEV could also be transmitted through blood. Moreover, HEV could be transmitted from the mother to the fetus, sexual intercourse, and injection (2,6). Studies focusing on the incidence of HEV infection in animals, especially pigs and wild boars, have demonstrated that the dairy and meat products of these animals may contribute to HEV transmission (7). On the other hand, transmission of HAV is easier and more widespread compared to HEV, which is associated with a higher risk of infection.

Despite general beliefs, HEV infection has a higher prevalence rate in industrialized countries compared to underdeveloped regions (8,9). According to statistics, Asia, Africa, the Middle East, and Central America account for the highest incidence rate of HEV infection (1,10,11). Hepatitis E is endemic in Iran, and several cases of HEV infection outbreak

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have been reported to date. One of the major risk factors for acute HEV infection is the consumption of undercooked meat or other unhealthy meat products (12).

Hepatitis E virus is the first and second most frequent cause of acute hepatitis in adult populations in Asia and the Middle East, respectively (13-15). Detection of the hepatitis E virus in serum and feces specimens is based on identifying the RNA virus, immunoglobulin G (IgG) or IgM antibodies against HEV. Currently, the gold standard for HEV detection for diagnostic and epidemiological purposes is serological and nucleic acid tests, which involve the qualitative and quantitative measurement of HEV RNA (16-18).

Some studies have reported that chronic HEV infection could improve after the reduction or discontinuation of immunosuppressive therapy (19,20) and replacement therapy with the oral administration of ribavirin (21,22) and pegylated interferon (23,24). However, there are no definite treatments for acute or chronic HEV infection in transplant patients. In such cases, hepatitis E may not lead to chronic hepatitis, with the exception of the patients with solid organ transplant or suppressed immune system (25,26).

As the most common type of acute adult hepatitis in developing countries, the prevalence of hepatitis E has recently been investigated widely. Of note, the prevalence of HEV varies depending on the geographical location. The present study aimed to systematically review the prevalence of HEV in Iran. The findings could lay the groundwork for further studies regarding the methods of effective prevention, treatment, and management of HEV epidemics.

Methods

Literature Search methods

A comprehensive systematic review was conducted in May 2016 via searching in databases such as PubMed, Scopus, and IranMedex using keywords such as “hepatitis E” and “prevalence” to assess the prevalence of hepatitis E infection in Iran. To do so, all the appropriate articles were identified by the following approach: (((Hepatitis E OR HEV)) AND (epidemiology OR frequency OR prevalence)) AND Iran. In the next step, a customized search was used to limit the records to the studies conducted on the Iranian population.

To reduce the possibility of data loss, the reference lists of all the included documents were manually searched for the potentially relevant articles. Finally, we searched in the Google Scholar using the aforementioned keywords in order to enclose the eligible documents in the review. Literature search procedures and qualitative data analysis were performed by two independent researchers.

Article selection

To conduct a comprehensive literature search, no time or language limitations were defined in selecting the related documents, and all the relevant articles published in English and Persian were included in the literature review. Articles with irrelevant subjects and those published in other languages were excluded from further evaluation. In addition, we removed editorials, review articles, meta-analyses, abstracts, and conference proceedings from the review. Among the other excluded cases were duplicate documents, articles reporting the data of the same populations, and articles with inappropriate or incomplete data. Finally, only the articles with appropriate data and study design focusing on the prevalence of HEV in various geographical regions of Iran were reviewed, and the articles with the following criteria were excluded.

Data extraction

Extracted data for the present review included the name of the authors, date of publication, total number of the studied samples, study design, and demographic data of the study populations. In addition, other data on the geographical region, evaluation methods, target populations, and major findings of the studies were collected and categorized. The estimated prevalence of HEV in the selected studies was recorded and described qualitatively. All the required data were extracted and qualitatively described based on the results of the studies reporting the prevalence of HEV infection in various geographical regions of Iran.

All the research processes, including the literature search, article selection, and data extraction were performed in accordance with the recommended protocol of the PRISMA 2009 Checklist for systematic reviews (27). Moreover, possible discrepancies between the authors were resolved prior to additional data processing.

Measured variables

The most important variables that were evaluated in the present review regarding the prevalence of HEV infection were anti-HEV IgG and IgM. Moreover, we assessed the prothrombin time and serum levels of other biochemical factors, including alanine transaminase, aspartate transaminase, alkaline phosphatase, albumin, direct and indirect bilirubin, and protein. It is also notable that the HEV RNA load was used in confirmatory testing in some of the selected studies, while biochemical tests and enzyme-linked immunosorbent assay (ELISA) were used in the evaluation of the required variables.

Results

Literature search results

In total, 46 potentially relevant articles were identified in the initial review search, 34 of which were in PubMed, nine were in Scopus, and three additional articles were found in IranMedex. According to the exclusion criteria of the study, 11 articles were eliminated after reviewing the titles and abstracts due to irrelevant subjects. Additionally, seven articles were excluded from further evaluation due to the inappropriate study design, and four documents were removed during data collection due to data inadequacy. Finally, the full texts of 24 articles, which focused on the prevalence of HEV in various geographical regions in Iran, were obtained and used for data extraction. Figure 1 depicts the procedures of literature search and article selection in the present study.

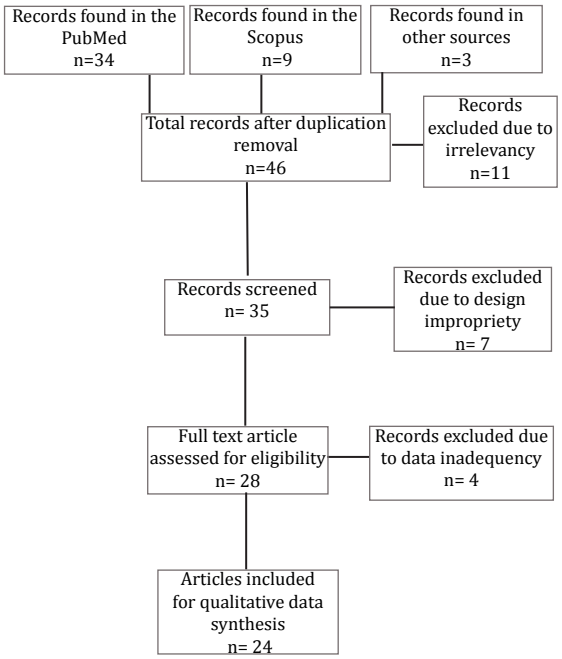

Figure 1. Flowchart of the literature search and strategy for the selection of relevant document.

General Features of the Selected Articles

Total number of the populations investigated in the selected articles focusing on the prevalence of HEV in Iran was 12,555 (range: 47-1,824). Studied populations included the patients with renal failure or end-stage renal disease (ESRD), pregnant women, blood donors, patients with HIV, patients undergoing chronic maintenance hemodialysis, renal transplant recipients, thalassemia patients, and general populations. Among these samples, 7,528 cases were male, and 5,027 cases were female. Age range of the studied populations in the selected studies was six months to 95 years.

The most recent reviewed article had been published in 2016, while the oldest article had been published in 2005. It is also noteworthy that all the selected studies that were used for qualitative data assessment were cross-sectional. The main features of the selected articles and their chronological date of publication are presented in Table 1.

Results of the Literature Review

After collecting the eligible articles, the extracted data were described qualitatively. According to the obtained results, the prevalence of the anti-HEV antibody is high in the Iranian population. The prevalence of HEV was observed to vary from 2.3% to more than 40% in the selected studies, with the highest and lowest rate reported in Ahvaz city located in Khuzestan province in the south-west of Iran (46.1%) and Sari city located in Mazandaran province in the north of Iran (2.3%), respectively (Table 2).

In the majority of the reviewed studies, sample populations consisted of patients with renal failure and those undergoing hemodialysis. Findings of the review indicated that male and female sample were susceptible to HEV infection since the anti-HEV IgG antibodies were detected in both genders with a similar prevalence (36,48). On the other hand, some studies reported the frequency of the anti-HEV IgG to be higher in male subjects compared to female subjects (44,49). Although the obtained results of some studies indicated that the prevalence of HEV increased with age (44,45,47,50), other research findings in this regard denoted no significant association between age and HEV prevalence since the rate of the infection was the same in earlier and older ages (46).

According to the results, the prevalence of HEV is higher in the rural areas of Iran compared to the urban areas (46). In addition, seroprevalence of HEV was observed to be high in the patients undergoing hemodialysis (33). While the qualitative assessment of the extracted data in the current review confirmed the relatively high prevalence of HEV in Iran, further comprehensive epidemiological studies are required in order to investigate the prevalence rate of this infection in the other geographical regions of Iran.

Figure 2 shows the prevalence of HEV in Iran. Studied variables, target populations, prevalence of HEV, and the main the findings of the reviewed studies are summarized in Table 2. According to this information and based on the IgG seroprevalence of HEV, the highest prevalence rate of HEV in Iran was observed in healthy populations (46.1%), kidney transplant patients (30.8%), and hemodialysis patients (28.3%), while the prevalence rate was found to be lower in pregnant women (3.6%).

Considering the high prevalence of HEV infection in various regions, it is recommended that diag

Table 1. General Information of Reviewed Articles.

NO	Author Reference	Year	Province	Mean age*	Male/Female Ratio	Number of participants
1	Sotoodeh Jahromi A. (28)	2016	Jahrom	NR	51/59	110
2	Hesamizadeh K. (29)	2016	Tehran	38	536/23	559
3	Naeimi B. (30)	2015	Bushehr	36.3	598/30	628
4	Joulaei (31)	2015	Shiraz	39.1	112/46	158
5	Alavian S.M. (32)	2015	Isfahan	53.23	285/264	549
6	Asaei S. (33)	2015	Shiraz	NR	725/305	1030
7	Farshadpour F. (34)	2015	Ahvaz	45.89	206/304	510
8	Eini P. (35)	2015	Hamadan	NR	83/70	153
9	Beladi Mousavi S.S. (36)	2014	Ahvaz	55.27	27/20	47
10	Rostamzadeh Khameneh Z. (37)	2013	Urmia	25.12	-/136	136
11	Ahmadi Ghezeldasht S. (38)	2013	Mashhad	29.06	718/864	1582
12	Sotoodeh Jahromi A. (39)	2013	Jahrom	35.42	447/30	477
13	Ramezani A. (40)	2013	Tehran	38	108/44	152
14	Ehteram H. (41)	2013	Kashan	36.3	487/43	530
15	Zekavat O.R. (42)	2013	Jahrom	52.61	234/122	356
16	Mobaien A.R. (43)	2013	Zanjan	57	49/44	93
17	Mohebbi S.R. (44)	2012	Tehran	41.28	200/351	551
18	Rostamzadeh Khameneh Z. (45)	2011	Urmia	35.4	61/30	91
19	Saffar M.J. (46)	2009	Sari	NR	565/515	1080
20	Ataei B. (47)	2009	Isfahan	NR	388/428	816
21	Taremi M. (48)	2008	Nahavand	34.7	799/1025	1824
22	Assarehzadegan M.A. (49)	2008	Ahwaz	33.3	260/140	400
23	Taremi M. (50)	2007	Tabriz	31.4	399/-	399
24	Taremi M. (51)	2005	Tabriz	53.5	190/134	324
* NR: Not reported.					Male: 7528 Female: 5027	Total= 12555

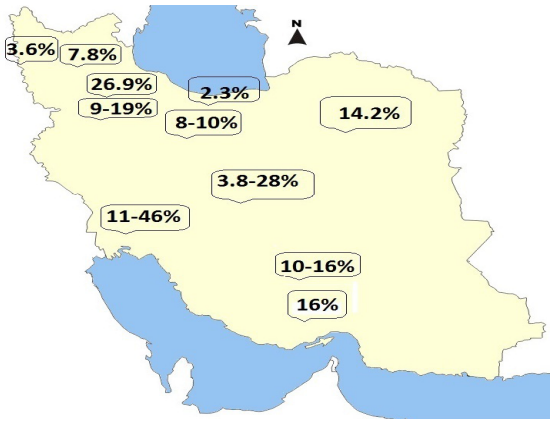

Figure 2. Prevalence of HEV in Various Geographical Regions of Iran.

Table 2. Main Findings and Reported Prevalence of HEV in Various Regions of Iran.

NO	Author Reference	Variables®	Target population *	Prevalence Rate(%)	Findings
1	Sotoodeh Jahromi A. (28)	HEV IgG and IgM	Thalassemia Patients	10 (IgG), 1.8 (IgM)	Prevalence of anti-HEV antibody was high in high-risk groups (thalassemia patients).
2	Hesamizadeh K. (29)	HEV IgG	Blood donors	8.1	HEV seroprevalence was significantly higher in regular and lapsed donors compared to first-time donors.
3	Naeimi B. (30)	HEV IgG	Blood donors	16.7	HEV seroprevalence was high among blood donors.
4	Joulaei H. (31)	HEV IgG	HIV patients	16.4	Seroprevalence of HEV was higher among HIV-infected patients in this study compared to the epidemiological studies on the general populations in Iran.
5	Alavian S.M. (32)	HEV IgG	Hemodialysis Patients	28.3	Seroprevalence of HEV was high in the hemodialysis units of Isfahan city.
6	Asaei S. (33)	HEV IgG and IgM	Hemodialysis Patients	13.4 (IgG), 0.9 (IgM)	Prevalence rates of HEV antibodies were positively correlated with age.
7	Farshadpour F. (34)	HEV IgG and IgM	Hemodialysis Patients	46.1 (IgG), 1.4 (IgM)	Seroprevalence of HEV IgG was high among adults.
8	Eini P. (35)	HEV IgG	Hemodialysis Patients	19.2	One in five patients undergoing maintenance dialysis in Hamadan city was seropositive for hepatitis E IgG antibody.
9	Beladi Mousavi S.S. (36)	LT, HEV IgG	ESRD patients	10.6	Prevalence of anti-HEV IgG antibody was high among the patients undergoing chronic hemodialysis.
10	Rostamzadeh Khameneh Z. (37)	LT, HEV IgG	Pregnant women	3.6	Seroprevalence of anti-HEV IgG was low among pregnant women.
11	Ahmadi Ghezeldasht S. (38)	LT, HEV IgG	General population	14.2	High prevalence of HEV was correlated with the populated district.
12	Sotoodeh Jahromi A. (39)	HEV IgG and IgM, ALT, AST	Blood donors	5.45	HEV was an etiological factor for hepatitis in Jahrom city.
13	Ramezani A. (40)	HEV IgG and IgM, ALT, AST	HIV patients	10	Seroprevalence of HEV was moderately high among HIV patients.
14	Ehteram H. (41)	HEV IgG	Blood donors	14.3	Prevalence of anti-HEV was relatively high among the blood donors in central Iran.
15	Zekavat O.R. (42)	HEV IgG, LT	Hemodialysis Patients	6.3% (patients), 2.9% (healthy individuals)	Anti-HEV prevalence was not significantly higher among the patients undergoing chronic hemodialysis.
16	Mobaien A.R. (43)	HEV IgG	ESRD patients	26.9	Prevalence of HEV was high in the hemodialysis patients in Zanjian city.
17	Mohebbi S.R. (44)	HEV IgG	General population	9.3	Seroprevalence of HEV antibodies was high, and HEV was endemic in this region.
18	Rostamzadeh Khameneh Z. (45)	HEV IgG	Kidney Transplant Patients	30.8	Anti-HEV IgG antibody had a high prevalence among the Iranian kidney transplant recipients.
19	Saffar M.J. (46)	HEV IgG	General population	2.3	Earlier age at exposure to infection and a higher infection rate were observed in the residents of rural areas compared to those in urban areas.
20	Ataei B. (47)	HEV IgG	General population	3.8	HEV seroprevalence was lower in Isfahan province compared to the previously reported rate in the other regions of Iran.
21	Taremi M. (48)	HEV IgG	General population	9.3	HEV infection had an average prevalence in Nahavand city.
22	Assarehzadegan M.A. (49)	HEV IgG	Blood donors	11.5	Anti-HEV had a high prevalence among blood donors, particularly males.
23	Taremi M. (50)	HEV IgG	Blood donors	7.8	High seropositive rate among male blood donors was compatible with the endemicity of HEV in Iran.
24	Taremi M. (51)	HEV IgG	Hemodialysis Patients	7.4	Prevalence of anti-HEV antibody was high among hemodialysis patients.

®HEV IgG: hepatitis E immunoglobulin G; HEV IgM: hepatitis E immunoglobulin M; LT: laboratory tests; ALT: alanine transaminase; AST: aspartate transaminase. *ESRD: end-stage renal disease

and general populations (2.3%).

Discussion

Seroepidemiological studies in developing countries have reported the prevalence rate of hepatitis E to be 10-35% in various geographical regions. However, in some reports, HEV has been considered to be the most common type of acute sporadic hepatitis among adults in developing countries (52).

Prevalence of HEV varies in different populations. According to the literature, several factors affect the prevalence rate of HEV infection, including lifestyle, environmental hygiene, contamination of the drinking water, race, gender, and age (53). Hepatitis E virus is known to be the most frequent cause of acute adult hepatitis in Asia, as well as the second cause of hepatitis in North Africa and the Middle East after hepatitis B (4,5).

Although the reported prevalence of HEV varied from 2.3% to more than 40% in the reviewed studies, the obtained results confirmed that HEV prevalence in Iran is as high as other countries, such as France, Italy, Denmark, Spain, India, and African countries (54). Outbreaks of this infection have been reported in the western and central regions Iran; in addition, the first and most important outbreak of HEV has been reported in Kermanshah, which is located in the west of Iran (55). The most recent outbreak of HEV was recognized in Lordegan region, located in Chaharmahal and Bakhtiari province in 2002 (55,56).

Several studies have investigated the prevalence of HEV in various regions in Iran. Accordingly, the prevalence rate of this infection varies in different geographical regions. Furthermore, the serological prevalence of anti-HEV antibodies differs in various countries. For instance, HEV prevalence has been estimated at 0.23% in the north-west of Greece (8), while has been reported to be near zero in Rio de Janeiro (Brazil) (57) and over 60% in Egypt (58,59).

According to the results of the current review, the prevalence of hepatitis E is higher in older populations, suggesting that the risk of HEV may increase with age (60). This is consistent with the findings of the present study as the reviewed articles revealed that HEV is more prevalent among the elderly (37,44,47).

As mentioned earlier, the prevalence of HEV varies in different geographical regions. Since we reviewed the reports from almost all the regions in Iran, our findings could determine the overall prevalence of HEV in Iran.

Considering the high prevalence of HEV infection in various regions, it is recommended that diagnostic tests for hepatitis E be carried out routinely, especially in the suspected cases of acute non-ABC hepatitis. Furthermore, performing other comprehensive studies across the country regarding the clinical manifestations and molecular features of this infection could yield detailed information on the epidemiology of HEV in Iran.

Conclusion

According to the results, the prevalence of HEV varies from 2.3% to more than 46% in the Iranian population. Additionally, data of the reviewed articles revealed that the prevalence of HEV is relatively low among pregnant women (3.6%), while the seroprevalence of HEV is estimated to be 2.3-46.1% in the healthy and general populations. In the patients with ESRD, the prevalence of HEV has been reported to be 10.6-26.9%. The reviewed studies denoted that the risk of HEV may increase with age. Moreover, the prevalence of HEV has been shown to be higher in hemodialysis patients.

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Conflict of Interest

The authors declare no conflict of interest.

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