

The prevalence of hepatitis E in Iran: systematic review of the literatures

Abstract

Background

Hepatitis E infection, which is caused by the hepatitis E virus (HEV), is a self-limiting disease with moderate to high prevalence in different areas. Since Iran is one of the areas where HEV is endemic, the aim of this study was to systematically review the prevalence of HEV in Iran.

Methods

A systematic search was performed on May 2016 in the PubMed, Scopus and IranMedex using following search method *((Hepatitis E OR HEV)) AND (epidemiology OR frequency OR prevalence)) AND Iran* to investigate the prevalence of Hepatitis E infection in Iran. After collection of the appropriate documents, the desired data were extracted and described.

Results

A total of 24 relevant articles with overall 12555 study population were collected. The results of this review showed that the prevalence of HEV was rather high among Iranian population. The prevalence of HEV varied between 2.3% to more than 40% among the studies.

Conclusion

Findings of this study showed that HEV prevalence is as same as those reported in other developing countries. The results of this study also necessitate the need to perform routinely diagnostic tests for the diagnosis of hepatitis E, especially in suspected cases of acute non A-B-C hepatitis.

Keywords: Hepatitis E virus, Non-A, non-B hepatitis

Introduction

Hepatitis E, which is generally a self-limiting disease, is caused by the hepatitis E virus (HEV) (1, 2). HEV is a single-stranded uncoated RNA virus and the only member of hepevirus species from Hepeviridae family (3, 4). Transmission of HEV, which was previously known as non-A, non-B hepatitis, is the same as hepatitis A virus (HAV) is through the water and feces (2). The importance of water in the transmission of virus is more than food (2, 3, 5). Studies have shown that the risk of HEV transmission may also be possible through blood. Other ways of transmission include through mother to fetus and sexually transmission in addition to injection (2, 6). Studies on the incidence of HEV infection in animals, especially pigs and wild boar have shown that their dairy and meat products may also contribute to transmission of HEV (7). However, HAV transmission is much easier and is also more widespread, which causes more infection. But, despite general belief, HEV infection is more commonly distributed in industrialized countries (8, 9). The highest incidence of HEV infection is in Asia, Africa, the Middle East and Central America (1, 10, 11). Iran is also one of the countries where hepatitis E is endemic and several cases of HEV infection outbreak have occurred so far. One of the major risk factors for acute infection with HEV is the consumption of undercooked meat or other meat products (12).

Hepatitis E virus is the first and second most common cause of acute hepatitis in adults in Asia and in the Middle East, respectively (13-15). Hepatitis E virus detection in the serum and feces specimens is mainly through detection of virus RNA or immunoglobulins (Ig) G or IgM antibodies against HEV. Currently, the gold standard test for HEV detection both for diagnostic and epidemiological purposes is serological and nucleic acid (qualitative and quantitative measurement of HEV RNA) tests (16-18). Although some studies have reported improvement of chronic infection after reduction or discontinuation of immunosuppressive therapy (19, 20), oral administration of ribavirin (21, 22) and PEGylated interferon was suggested (23, 24).

But, there is no proven treatment for acute or chronic hepatitis E virus in transplant patients. Hepatitis E does not usually cause a chronic hepatitis except for those who have had a solid organ transplant or their immune system is suppressed (25, 26).

The prevalence of hepatitis E as the most common type of acute adult hepatitis in developing countries has been recently taken into consideration. The prevalence of HEV differs in different geographical area. In this study, we aimed to systematically review the prevalence of HEV in Iran. The results of this study can be a basis for further studies on methods for prevention and therapy in addition to dealing with HEV epidemics.

Methods

Search methods

A comprehensive systematic search was conducted in the PubMed, Scopus and IranMedex using "*Hepatitis E*" and "*prevalence*" as search terms to study the prevalence of Hepatitis E infection in Iran on May 2016. For this purpose, following search method (*((Hepatitis E OR HEV)) AND (epidemiology OR frequency OR prevalence)) AND Iran* was used to find all potentially appropriate articles. By using a customized search, the search records were then limited to only articles conducted on Iranian population. To reduce the possibility of data loss, the reference lists of all included documents were manually searched for potentially relevant articles. Finally, Google scholar was also searched using the aforementioned search terms to include all eligible documents. All procedures of literature search and qualitative analysis of data were performed by two independent authors.

Study selection

To perform a comprehensive literature search, no time or language limitation was defined during study selection, and all articles with English and Persian language that were relevant to

the purpose of this study were included in this literature review. Articles with subject and language irrelevancy were eliminated in the first step. Afterwards, editorials, review articles and meta-analysis as well as abstracts and conference proceedings were excluded from further processing. Likewise, duplicated documents or articles wherein the data of the same population had been reported were also excluded. Articles with inappropriate or incomplete data were also excluded from further assessment. Therefore, according to aforementioned all articles with appropriate data and study design wherein the prevalence of HEV had been investigated in different geographical regions of Iran were included, and articles with the following criteria were excluded from further processing:

- I. Article with language other than English and/or Persian
- II. Editorials, case series, abstracts and review articles
- III. Articles with subject irrelevancy or data insufficiency
- IV. Duplicated documents

Data extraction

Information including author's name, publication date, total number of studied population, and the type of study design as well as demographic data of studied population were extracted. In addition, other data including geographical region, methods of assessment, target population, and the major findings of each study were collected and categorized. The prevalence of HEV in each study was recorded and qualitatively described. All the desired data were extracted and qualitatively described based on the results of articles reporting the prevalence of HEV infection in geographical regions of Iran. All processes of this review including literature search and selection, in addition to data extraction were performed according to the recommended protocol of PRISMA checklist 2009 for systematic reviews (27). Any possible discrepancies between the authors were also resolved prior to additional data processing.

Measured variables

The most important variables that had been evaluated in the included literatures included anti-HEV IgG, and IgM. However, the serum level of other biochemical factors including alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), albumin, direct and indirect bilirubin levels, serum protein and prothrombin time (PT) had also been evaluated. In addition, RNA load of HEV was as confirmatory tests in some studies. On the other hand, biochemical tests and enzyme-linked immune sorbent assay (ELISA) had been assisted for evaluation of the desired variables.

Results

Literature search results

Of total of 46 potentially relevant articles, 34 were in the PubMed, and 9 in the Scopus. Three additional articles were also found in IranMedex. According to exclusion criteria, 11 articles were crossed out after reviewing the title and abstract of the collected articles due to subject irrelevancy. Other 7 articles were further excluded from additional assessment due to design inappropriacy. Four documents were also excluded during data collection due to data inadequacy. Finally, full text of 24 articles wherein the prevalence of HEV had been reported in different geographical regions of Iran were collected and used for further data extraction. Figure 1 shows the full procedure of literature search and article selection.

General characteristics of the included articles

The total number of population that had been enrolled in the selected articles wherein the prevalence of HEV had been evaluated in Iran was 12555. Their number varied from 47 to 1824. Studied populations in the selected literature included patients with renal failure or with end stage renal disease (ESRD), pregnant women, blood donors, HIV-infected patients,

patients with chronic maintenance hemodialysis, renal transplant recipients, thalassemia patients and general population. Of these patients, 7528 were male and 5027 were female. The age of enrolled populations varied from six months old children to 95 years. The most recent and old articles included in this literature review had been published in 2016 and 2005, respectively. The collected articles that were used for qualitative data assessment were all cross-sectional studies. The major characteristics of included literatures are demonstrated in **Table 1** in their chronological order of published time.

Study results

After collection of the eligible articles, the data were extracted were then qualitatively described. The results of studies showed that the prevalence of anti-HEV antibody was high among Iranian population. The prevalence of HEV varied between 2.3% to more than 40% among the studies. The highest and lowest prevalence of HEV were reported from Ahvaz (Khuzestan province, South West of Iran) with 46.1% and Sari (Mazandaran province, North of Iran) with 2.3%, respectively (**Table 2**). The most studied population were patients with renal failure and hemodialysis patients. Findings showed that both males and female are susceptible to this infection, since anti-HEV IgG antibodies were found in both gender with almost same prevalence (36, 48). But some studies showed that the prevalence of anti-HEV IgG was greater among men than women (44, 49). Moreover, although the results showed that the prevalence of HEV increased with age (44, 45, 47, 50), but findings of other studied concluded that there is no significant association between the age and prevalence of HEV, since the occurrence of infection in earlier age has the same prevalence as for in older age (46).

On the other hand, findings showed that the prevalence of HEV was higher in rural areas than in urban areas (46). In addition, the seroprevalence of HEV was found to be high in hemodialysis patients (33). Therefore, qualitative assessment of extracted data showed that the

prevalence of HEV was rather high in Iran; however, further comprehensive epidemiological studies are recommended to investigate the prevalence of HEV in different geographical regions of Iran. The prevalence of HEV in Iran is demonstrated in **Figure 2**. Studied variables, target population, prevalence of HEV, and main the findings of each study are also summarized in **Table 2**. According to aforementioned and based on IgG seroprevalence of HEV, the highest prevalence of HEV in Iran was observed in healthy population (46.1%), kidney transplant (30.8%), and hemodialysis patients (28.3%), while the prevalence of HEV was lower in pregnant women (3.6%), and general population (2.3%).

Discussion

Seroepidemiological studies in developing countries show that the prevalence of hepatitis E is from 10% to 35% in different geographical regions. However in some reports, HEV is considered as the most common type of acute sporadic hepatitis of adults in developing countries (52). The prevalence of HEV varies among the population. Studies have suggested that many factors including life style, environmental hygiene, contamination of drinking water, race, gender, and age may affect the rate of HEV infection (53). Hepatitis E virus is known as the most common cause of acute adult hepatitis in the Asia and the second cause of hepatitis in North Africa and the Middle East after hepatitis B (4, 5). Although the reported prevalence of HEV varied between 2.3% to more than 40% among the studies; however, the results of this study show that HEV prevalence in Iran is as high as those reported in other countries such as France, Italy, Denmark, Spain, India, and African countries (54). Outbreaks of this disease have been reported from the west and central Iran; in addition, the first and most important outbreak of HEV have been reported from Kermanshah, west of Iran (55). The last known outbreak of HEV was also reported from Lordegan of Chaharmahal and Bakhtiari province in 2002 (55, 56).

Many studies have been conducted on the prevalence of HEV in different areas of Iran. The results of these studies show that HEV prevalence differs in different geographical regions. Serological prevalence of anti HEV antibodies also differ in different countries. For example, HEV prevalence was 0.23% in North West Greece (8), near to zero in Rio de Janeiro, Brazil (57) and over 60% in Egypt (58, 59). The results also show that the prevalence of hepatitis E is higher in older population, suggesting that the risk of HEV may increase with increasing the age (60). These results are consistent with the findings of this study wherein the included studies have shown that HEV is more prevalent in elderly (37, 44, 47).

The results of this review showed that the prevalence of HEV differs in different geographical regions of Iran. But, it was shown that HEV prevalence is as same as those reported in other developing countries. Since this study contained reports from almost all area of Iran, the findings of this review may show the overall prevalence of HEV in Iran. Given the high prevalence of HEV infection in different areas, it is suggested to routinely perform diagnostic tests for the diagnosis of hepatitis E, especially in suspected cases of acute non A-B-C hepatitis. Also, it is necessary to perform other comprehensive studies across the country on clinical manifestation of the disease and molecular characteristics of the HEV to obtain more detailed information about the epidemiology and infection of HEV in Iran.

Conclusion

The results of this review showed that the prevalence of HEV varies between 2.3% to more than 46% among Iranian population. Also, it was shown that the prevalence of HEV is low among women (3.6%), while seroprevalence of HEV varied between 2.3% to 46.1% among healthy and general population. HEV prevalence also varied between 10.6% to 26.9% among patients with ESRD. Findings also demonstrated that the risk of HEV may increase with age. In addition, HEV prevalence was shown to be higher in hemodialysis patients.

References

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Uncorrected Proof

Table 1. General information of the included literatures.

No	First author	Year	Province	Mean age*	Sex ratio Male/female	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 H (31)	2015	Shiraz	39.1	112/46	158
5	Alavian SM (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 SS (36)	2014	Ahvaz	55.27	27/20	47
10	Rostamzadeh Khameneh Z (37)	2013	Urmia	25.12	-/136	136
11	Ahmadi Ghezdasht 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 OR (42)	2013	Jahrom	52.61	234/122	356
16	Mobaien AR (43)	2013	Zanjan	57	49/44	93
17	Mohebbi SR (44)	2012	Tehran	41.28	200/351	551
18	Rostamzadeh Khameneh Z (45)	2011	Urmia	35.4	61/30	91
19	Saffar MJ (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 MA (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	N= 12555

Table 2. The main findings and the reported prevalence of HEV in different areas of Iran.

No	First author	Variables®	Target population *	Prevalence (%)	Findings
1	Sotoodeh Jahromi A (28)	HEV Ig-G and Ig-M	Th patients	10 (Ig-G), 1.8 (Ig-M)	Prevalence of anti-HEV antibody is high in high risk groups such as thalassemia patients.
2	Hesamizadeh K (29)	HEV Ig-G	Blood donors	8.1	HEV seroprevalence was significantly higher in regular and lapsed donors than in first-time donors.
3	Naeimi B (30)	HEV IgG	Blood donors	16.7	High HEV seroprevalence was observed among the blood donors.
4	Joulaei H (31)	HEV IgG	HIV patients	16.4	Seroprevalence of HEV among HIV infected patients in this study was higher than epidemiological studies of general populations of Iran.
5	Alavian SM (32)	HEV IgG	HD patients	28.3	Seroprevalence of HEV is high in Isfahan hemodialysis units.
6	Asaei S (33)	HEV Ig-G and Ig-M	H people	13.4 (Ig-G), 0.9 (Ig-M)	The prevalence rates of HEV antibodies were positively correlated with age.
7	Farshadpour F (34)	HEV Ig-G and Ig-M	H people	46.1 (Ig-G), 1.4 (Ig-M)	High HEV IgG seroprevalence of was observed among adults.
8	Eini P (35)	HEV IgG	HD patients	19.2	One in five patients undergoing maintenance dialysis in Hamadan is seropositive for hepatitis E Ig-G antibody.
9	Beladi Mousavi SS (36)	LT, HEV IgG	ESRD patients	10.6	The prevalence of anti-HEV IgG antibody was high among chronic HD patients.
10	Rostamzadeh Khameneh Z (37)	LT, HEV IgG	Pregnant women	3.6	Seroprevalence of anti-HEV IgG is low in the population of pregnant women.
11	Ahmadi Ghezeldasht S (38)	LT, HEV IgG	General population	14.2	High prevalence of HEV is related to populated district.
12	Sotoodeh Jahromi A (39)	HEV Ig-G and Ig-M, ALT, AST	Blood donors	5.45	HEV is an etiological factor for hepatitis in Jahrom.

13	Ramezani A (40)	HEV Ig-G and Ig-M, ALT, AST	HIV patients	10	Seroprevalence of HEV was moderately high in HIV patients.
14	Ehteram H (41)	HEV Ig-G	Blood donors	14.3	Relatively high prevalence of anti-HEV was observed in the blood donors of central Iran.
15	Zekavat OR (42)	HEV Ig-G, LT	HD patients	6.3% (patients), 2.9% (healthy people)	Significant higher anti-HEV prevalence was not observed among patients with chronic hemodialysis.
16	Mobaien AR (43)	HEV Ig-G	ESRD patients	26.9	Prevalence of HEV in hemodialysis patients was high in Zanzjan.
17	Mohebbi SR (44)	HEV Ig-G	General population	9.3	Seroprevalence of HEV antibodies is high and HEV is endemic in this region.
18	Rostamzadeh Khameneh Z (45)	HEV IgG	KT patients	30.8	The anti-HEV IgG antibody has a high prevalence in Iranian kidney transplant recipients.
19	Saffar MJ (46)	HEV IgG	General population	2.3	Earlier age at exposure to infection and a higher infection rate were found in people residing in rural areas than in urban areas.
20	Ataei B (47)	HEV IgG	General population	3.8	HEV seroprevalence in Isfahan Province is lower than that previously reported in other parts of Iran.
21	Taremi M (48)	HEV IgG	General population	9.3	HEV infection is of intermediate prevalence in Nahavand.
22	Assarehzadegan MA (49)	HEV IgG	Blood donors	11.5	High prevalence of anti-HEV was observed among blood donors, particularly males.
23	Taremi M (50)	HEV IgG	Blood donors	7.8	High seropositive rate among male blood donors is compatible with endemicity of HEV in Iran.
24	Taremi M (51)	HEV IgG	HD patients	7.4	Prevalence of anti-HEV antibody was high in 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, KT: Kidney transplant, Th: Thalassemia, HD: Hemodialysis, H: Healthy.

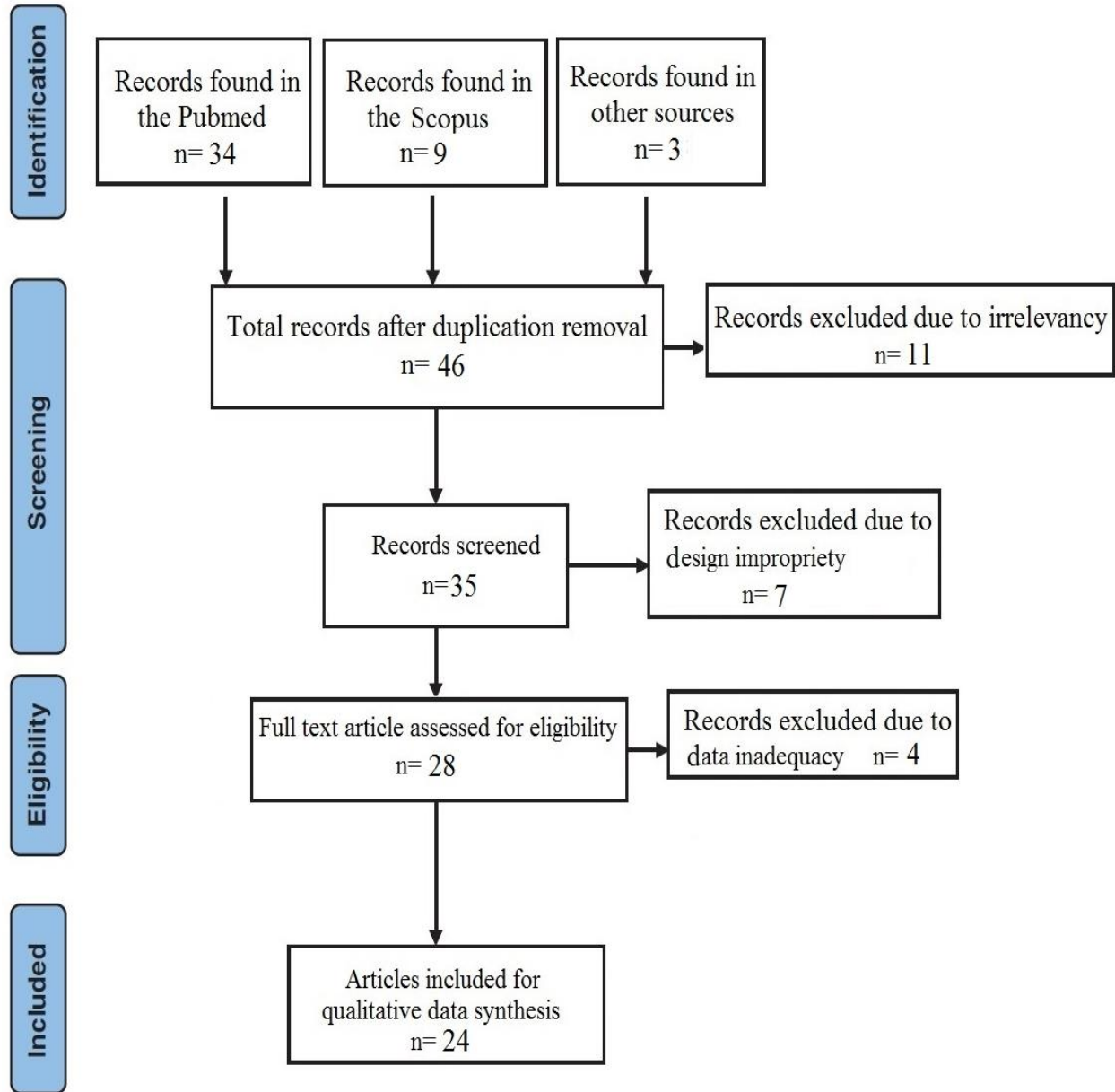


Figure 1. Flowchart of the literature search and strategy for the selection of relevant document.

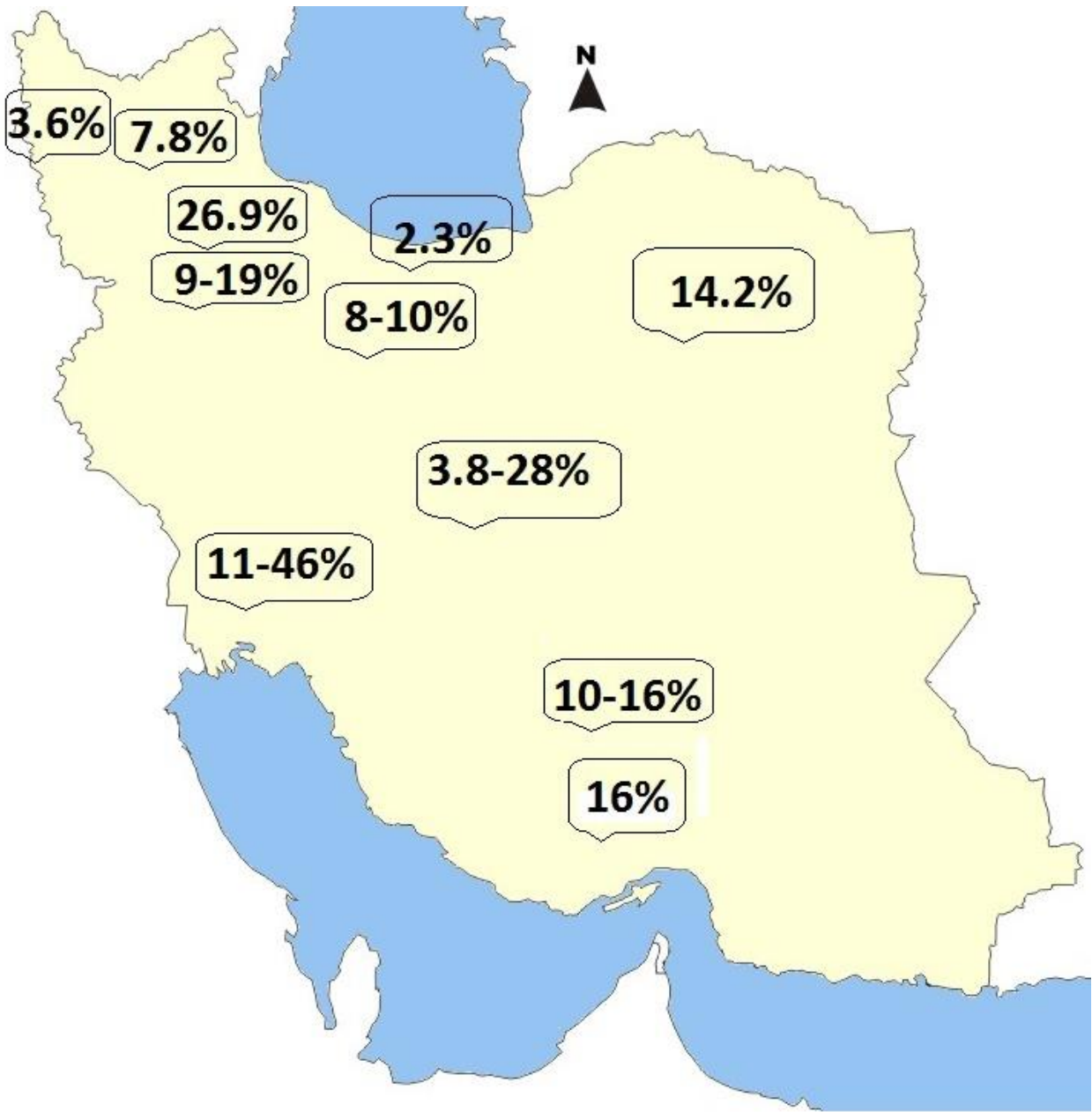


Figure 2. The prevalence of HEV in different geographical regions of Iran.