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Seroprevalence and geographical distribution of hepatitis C virus in Iranian patients with thalassemia: a systematic review and meta-analysis

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Abstract

Background: Thalassemia as a hereditary hemoglobinopathy is the most common monogenic disease worldwide. Patients with thalassemia require regular blood transfusion, which provides the risk for the transmission of hepatitis C virus (HCV) as the most common post-transfusion infection in such patients, and this rate is very diverse in different parts of the world. We aimed to determine the prevalence of HCV among patients with thalassemia in Iran.

Methods: In this study, we searched for articles on the prevalence of HCV among Iranian thalassemia patients in English and Persian databases up to 2017. Heterogeneities were assessed by using an *I*-square (I^2) test. Prevalence and 95% confidence interval (CI) were calculated using the random effects model.

Results: In total, 37 studies with 9185 patients were included in the meta-analysis. The prevalence of HCV among Iranian thalassemia patients was 17.0% (95% CI: 14.5–19.8). The rate of prevalence among male and female subjects was 17.4% (95% CI: 13.8–21.9) and 16.8% (95% CI: 13.2–21.1), respectively.

Conclusions: We found that the prevalence of HCV among Iranian thalassemia patients declined over time and the Iranian Blood Transfusion Organization has had a reasonable performance in HCV screening.

Keywords: blood transfusion; β-thalassemia; hepatitis C virus; meta-analysis.

Background

Thalassemia, the most common human monogenic disease worldwide is caused by mutations in globin genes related to the lack or reduced production of α- or β-globin chains [1]. Thalassemia patients have various degrees of anemia from mild to intrauterine death that requires different plans for blood transfusion [2]. Moreover, it is interesting to note that, β-thalassemia being homozygous causes the main clinical problems [3–5]. The prevalence of thalassemia in populations of the Mediterranean region and the Middle East, is significantly high. Annually worldwide, about 56,000 β-thalassemia major cases are identified or born, of which, more than 50,000 are the newborns and according to the World Health Organization (WHO), 30,000 of whom need the regular blood transfusions [1, 2, 6].

Thalassemia is one of the most important health problems in Iran, because it is located in the central part of the region that is called "*The Thalassemia Belt*". Studies indicate that there are more than 25,000 cases of thalassemia major in Iran [7, 8].

Given that the majority of patients with severe thalassemia need regular blood transfusions, the risk of

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transmission of viral infections is greater than in healthy individuals. The most common post-transfusion infection is hepatitis C virus (HCV), a single-stranded RNA virus of the *Flaviviridae* family that may cause chronic hepatitis, cirrhosis and hepatocellular carcinoma. According to the WHO, about 3% (170 million people) of the population in the world are infected with this infection [9–11]. Studies on the prevalance of this infection in patients with β-thalassemia revealed an occurrence from 3% to 67.3% [8, 12–16].

The prevalence of HCV infection in thalassemia patients is reported from 2 to 32% in Iran. However, it is somewhat interesting to note that these screening studies do not give us a clear picture and they do not provide comprehensive information that can be generalized to society. Moreover, the different indicators in various studies have different effects. The reasons for these differences are unknown; probably, regional differences, sampling, time and duration of screening, and factors involved in data analysis play a major role in these research gaps. Besides, most studies were performed on a small number of patients that can indicate the reasons for differences in the studies. The objective of this study is to use meta-analysis for the regularization of numerical data reported in previous studies on the prevalence of HCV in patients with thalassemia to overcome the limitations of these studies.

Methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used to design, analyze and report the obtained data. We conducted a systematic search for the relevant articles from March 21 to April 9, 2017 using the databases of PubMed, Scopus, Google Scholar (searched in title) and Scientific Information Database (SID) (all fields) and the Science Direct website, which together cover all medical journals and other publications related to the topic.

The search process was done by two researchers using the following keywords: intervention ("HCV" OR "Hepatitis C Virus") AND ("Anti-HCV" OR "Anti-HCV Antibodies" OR "Anti-Hepatitis C Virus Antibodies") AND "Thalassemia" AND "Prevalence" AND "Iran". The search strategy included both English and Persian articles. Moreover, we used the references of collected studies to find data that may not have been found in our search.

Criteria for including studies

All papers, which included the mentioned keywords were screened by two researchers and selected papers were scanned by checking the title and abstract for inclusion or exclusion from the study. Inclusion criteria of our study were all observational research published in English or Persian that reported the prevalence of HCV based on HCV antibody immunoassay among patients with thalassemia in different parts of Iran. Exclusion criteria included papers that were not conducted in Iran, were not done on patients with thalassemia, and did not report the prevalence of HCV and studies that had incomplete data for any reason.

To extract data from the papers, we designed a checklist including author names, study region, date, the number of patients, the number and percentage of males and females, the mean age of cases the prevalence of positive anti-HCV.

At the end of the search, 215 papers were obtained. Of them, 50 papers were irrelevant to the topic, 80 studies were duplicated by checking titles and abstracts, three papers were not conducted in Iran, 33 papers were not original studies, the data from seven studies were incomplete, and in five studies the same data were repeated. Finally, 37 papers were included into current meta-analysis.

Quality assessment

Two members of our team independently valued the selected articles using the standard 22-item Strengthening The Reporting of OBservational Studies in Epidemiology (STROBE) checklist in relation to various aspects of methodology and study process [17]. The supervisor of the study solved any disagreements. A score between 0 and 7 was considered low quality (C), 8 and 14 as moderate (B), and 15 and 22 as high quality (A).

Data analysis

In this study, we aimed to determine the prevalence of HCV among Iranian patients with thalassemia. All statistical analyses were done using the Comprehensive Meta-Analysis version 2.2.064 (CMA) [18]. p-Values less than 0.05 were considered statistically significant. Heterogeneities were evaluated using an *I*-square (I^2) test [19]. Because of significant heterogeneity calculated for results, the random effects model, which takes the diversity of the studies into account was used [20].

Results

Information from studies included into the meta-analysis

In this systematic review, 215 papers were identified and retrieved from the databases and after the final evaluation, 37 papers passed through the checklist, and the full text of the papers was assessed. The PRISMA Flow Diagram of search strategy is shown in Figure 1. The final studies were published during the years 2000–2017, and a total of 9185 individuals participated in these studies. A summary of the information provided by the studies is presented in Table 1.

Meta-analysis results

Based on these articles, the mean prevalence of hepatitis C infection in patients with thalassemia was 17.0% [95% confidence interval (CI): 14.5–19.8, $I^2 = 89.874\%$, $p = 0.000$] (Figure 2). The prevalence of HCV in thalassemia male patients was 17.4% (95% CI: 13.8–21.9, $I^2 = 83.275\%$, $p = 0.000$) and in females was 16.8% (95% CI: 13.2–21.1, $I^2 = 82.600\%$, $p = 0.000$). Separate information on male and female patients is presented in Table 1 and Figure 3. In addition, Egger's test results indicated no significant publication bias ($p = 0.185$) (Figure 4).

Distribution map

To illustrate the distribution of HCV prevalence in patients with thalassemia in different provinces of Iran, Excel 2016 software was used to design the map of Iran. A meta-analysis was conducted on the provincial prevalence that had been studied several times. Two multicenter studies in which the details of the prevalence were not reported by region were not included in the design of this map. No reports were found in the parts of the map that are colorless

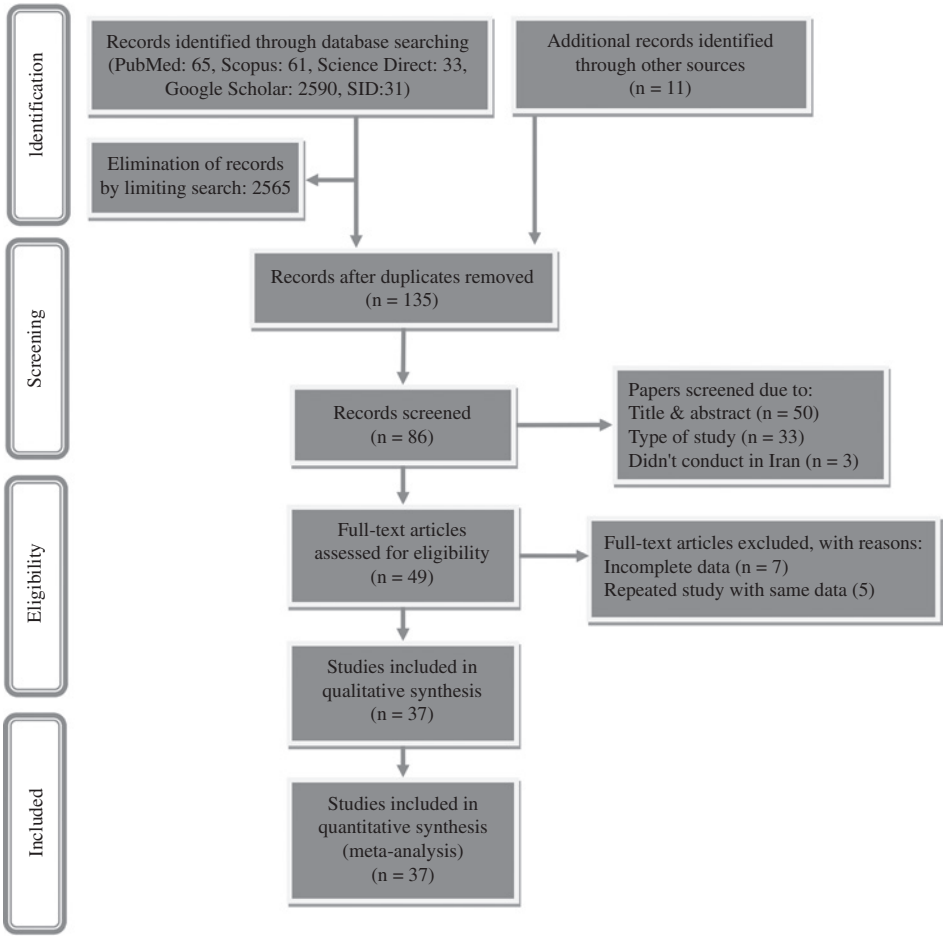

Figure 1: PRISMA flowchart for search strategy and study selection.

Table 1: Characteristics of studies included in the systematic review and meta-analysis after complete evaluation.

Study	Reference	Publication year	Study period	Region	NP	Male, n (%)	Female, n (%)	Age, mean, years	Anti-HCV+ n, (%)	STROBE score (classification)[a]
Vahidi et al.	[21]	2000	1996	Kerman	107	59 (54.90)	48 (44.80)	9.24	24 (22.40)	17(A)
Najafi et al.	[22]	2001	1998	Mazandaran	100	49 (49.00)	51 (51.00)	11.96	18 (18.00)	12(B)
Basirat nia	[23]	2001	1999	Chaharmahal and Bakhtiari	113	63 (55.70)	50 (44.30)	NR	26 (23.00)	12(B)
Karimi and Ghavanini	[24]	2001	1999–2000	Fars	466	243 (52.10)	223 (47.90)	11.70	73 (15.70)	15(A)
Nakhaie and Talachian	[25]	2003	1999–2000	Tehran	507	NR	NR	NR	122 (24.00)	13(B)
Sanei Moghaddam et al.	[26]	2004	2002	Sistan and Baluchestan	364	206 (56.60)	158 (43.40)	9.7	49 (13.46)	13(B)
Alavi et al.	[27]	2005	2002	Tehran	110	55 (50.00)	55 (50.00)	11.50	13 (11.80)	12(B)
Faranoush et al.	[28]	2005	2002	Semnan	63	40 (60.40)	23 (39.60)	11.80	25 (39.60)	13(B)
Torabi et al.	[29]	2005	2003	East Azerbaijan	84	50 (59.50)	34 (40.50)	11.50	6 (7.10)	12(B)
Javadzadeh et al.	[30]	2006	2003	Yazd	85	41 (48.20)	44 (51.80)	12.60	8 (9.40)	15(A)
Mirmomen et al.	[31]	2006	2002	Multicenter[b]	732	413 (56.40)	319 (43.60)	17.90	141 (19.20)	13(B)
Ghafourian et al.	[32]	2006	1999–2004	Khuzestan	122	73 (59.80)	49 (40.20)	14.96	32 (26.20)	16(A)
Ansari et al.	[33]	2007	2005–2006	Fars	806	406 (50.40)	400 (49.60)	15.3	116 (14.40)	15(A)
Company et al.	[34]	2007	2005–2006	Khuzestan	195	98 (50.25)	197 (49.75)	14.97	40 (20.50)	16(A)
Ahmad et al.	[35]	2007	2003–2004	Fars	200	100 (50.00)	100 (50.00)	NR	50 (25.00)	15(A)
Samimi-Rad and Shahbaz	[36]	2007	2004	Markazi	98	50 (51.00)	48 (49.00)	13.1	5 (5.10)	12(B)
Kashef et al.	[37]	2008	2008	Fars	131	63 (48.10)	68 (51.90)	14.6	24 (18.32)	12(B)
Arababadi et al.	[38]	2008	2006–2007	Kerman	60	NR	NR	12.1	27 (45.00)	12(B)
Ameli et al.	[39]	2008	2006	Mazandaran	65	NR	NR	19.51	11 (16.90)	16(A)
Mahdaviani et al.	[40]	2008	2004	Markazi	97	50 (51.50)	47 (48.50)	13.1	7 (7.20)	14(B)
Bozorgi et al.	[41]	2008	2004	Qazvin	207	99 (48.30)	104 (51.70)	14.29	52 (25.10)	12(B)
Hassanshahi et al.	[42]	2009	2006–2007	Kerman	181	81 (45.10)	100 (54.90)	14.5	81 (44.80)	18(A)
Azarkar et al.	[43]	2009	2007	South Khorasan	38	21 (54.10)	17 (45.90)	9.2	0 (0.00)	10(B)
Ghafourian et al.	[44]	2009	2006–2007	Khuzestan	206	97 (47.10)	109 (52.90)	18.98	58 (28.15)	12(B)
Sammak et al.	[45]	2010	2007	Qom	142	76 (53.50)	66 (46.50)	14.3	19 (13.40)	11(B)
Raeisi et al.	[46]	2011	2005	Chaharmahal and Bakhtiari	91	41 (45.00)	50 (55.00)	13.2	19 (21.00)	10(B)
Ghane et al.	[47]	2011	2011	Multicenter[c]	245	125 (51.00)	120 (49.00)	18.38	28 (11.40)	15(A)
Kashanchi et al.	[48]	2011	2009–2010	Alborz	206	90 (43.70)	116 (56.30)	19.64	31 (15.00)	13(B)
Kalantari et al.	[49]	2011	2008–2010	Isfahan	545	312 (57.20)	233 (42.80)	18	50 (9.10)	18(B)
Azarkeivan et al.	[50]	2012	1996–2009	Tehran	395	229 (58.00)	166 (42.00)	27.5	109 (27.60)	11(B)
Alavi et al.	[51]	2012	2011	Tehran	90	46 (51.10)	44 (48.90)	14.1	12 (13.30)	14(B)
Ataei et al.	[52]	2012	1996–2011	Isfahan	463	270 (58.30)	193 (41.70)	17.46	37 (7.90)	14(B)
Sarkari et al.	[53]	2012	2009–2010	Kohgiluyeh and Boyer-Ahmad	49	NR	NR	NR	3 (6.10)	16(A)
Jafroodi et al.	[8]	2015	2002–2012	Gilan Province	1113	535 (48.10)	578 (51.90)	22.93	152 (13.60)	18(A)
Valizadeh et al.	[7]	2015	2014	West Azerbaijan	32	18 (56.25)	14 (43.75)	11.41	0 (0.00)	10(B)
Bazi et al.	[54]	2016	2014	Sistan and Baluchestan	90	46 (51.10)	44 (48.90)	14.8	9 (10.00)	11.(B)
Aminianfar et al.	[55]	2017	2014–2015	Hormozgan	587	280 (47.70)	307 (52.30)	31	60 (10.22)	15(A)

NP, number of patient; NR, not reported. [a]Classification: 0–7(C), 8–14(B), 15–22(A). [b]Tehran, Kerman, Qazvin, Semnan, and Zanjan. [c]Gilan and Mazandaran.

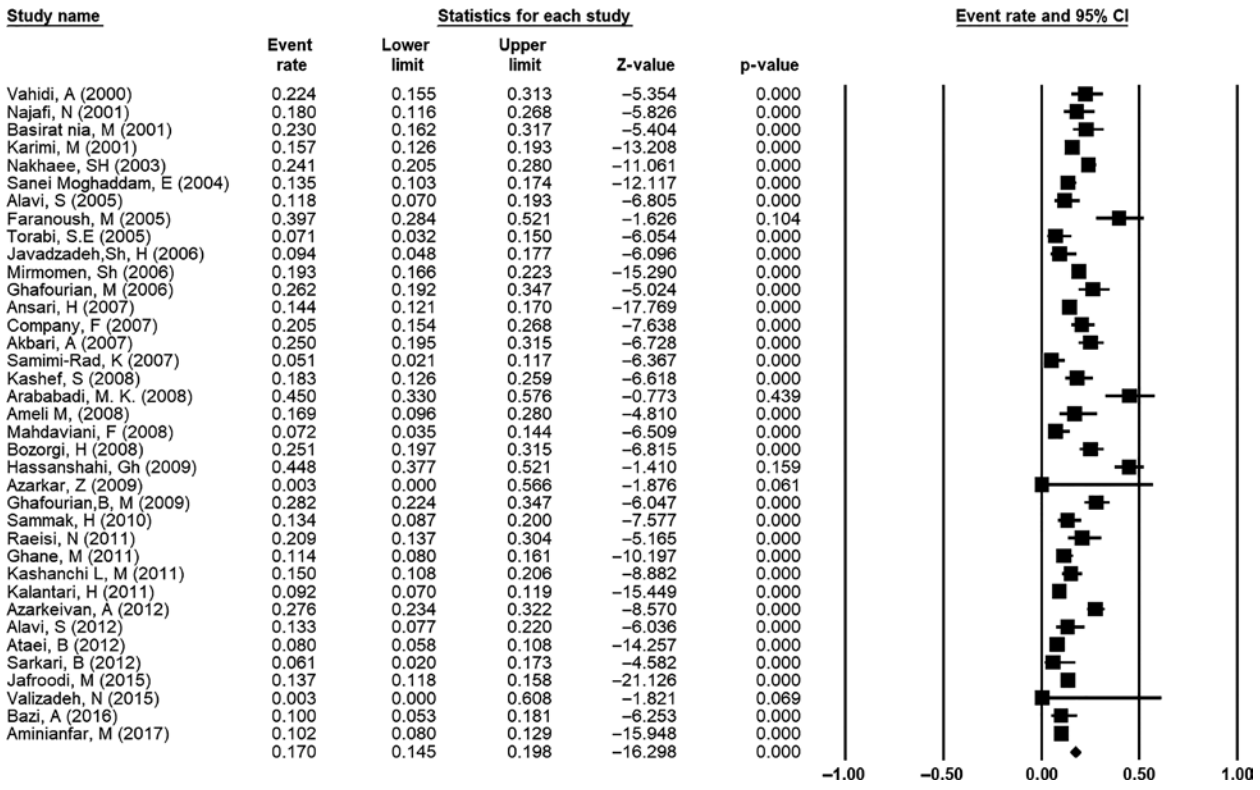

Figure 2: Forest plot of meta-analysis on the prevalence of hepatitis C infection in patients with thalassemia in Iran with 95% CI. Each horizontal bar shows the length of the CI. The diamond shape at the end of the figure shows the pooled prevalence based on random-effects models.

including Ardabil, Bushehr, Golestan, Hamadan, Kermanshah, Kurdistan, Lorestan, North-Khorasan, Razavi-Khorasan and Ilam. Details are presented in Figure 5.

Discussion

The importance of HCV prevalence in patients with thalassemia and various reports of this prevalence in Iran followed by a mismatch between different studies made us perform this systematic review and meta-analysis to overcome the limitations of previous studies. This study was accomplished to estimate the prevalence and distribution of HCV among patients with thalassemia in Iranian population based on the available data extracted from all studies conducted in different parts of Iran for the first time.

The results of the meta-analysis on a combination of data from 37 studies showed the prevalence of HCV among patients with thalassemia in Iran is approximately 17.0% (95% CI: 14.5–19.8), which is nearly consistent with another review published by Alavian et al. in 2010 [56]. A comparison of the prevalence of HCV between these two studies shows that there has not been an increasing trend, implying that blood transfusion organization has had an reasonable performance regarding the management of HCV.

There are also contraindicating reports on the rate of prevalence in studies conducted in different parts of the world, for example, the prevalence of HCV among Egyptian, Taiwanese, Thai, Italian, Jordanian, Pakistan and eastern India thalassemia patients was reported 45.50%, 37.30%, 20.20%, 56.30%, 40.5%, 49% and 24.6%, respectively [57–63]. Although our overall prevalence is lower than these reports, most of the studies we have reviewed is consistent with the mentioned studies from the other countries. To the best of our knowledge, there are no comprehensive studies on this topic worldwide. Moreover, the other remarkable thing is that most of these studies, regardless of the location of the research, have been conducted on a small sample size and are completely out of date. Hence, the gap of comprehensive local, national and global epidemiological studies is completely obvious.

The prevalence of HCV in male and female thalassemia patients was 17.4% (95% CI: 13.8–21.9) and 16.8% (95% CI: 13.2–21.1), respectively. This can be due to the weakness of the men's immune system in comparison to the women in relation to HCV, which has not been confirmed specifically

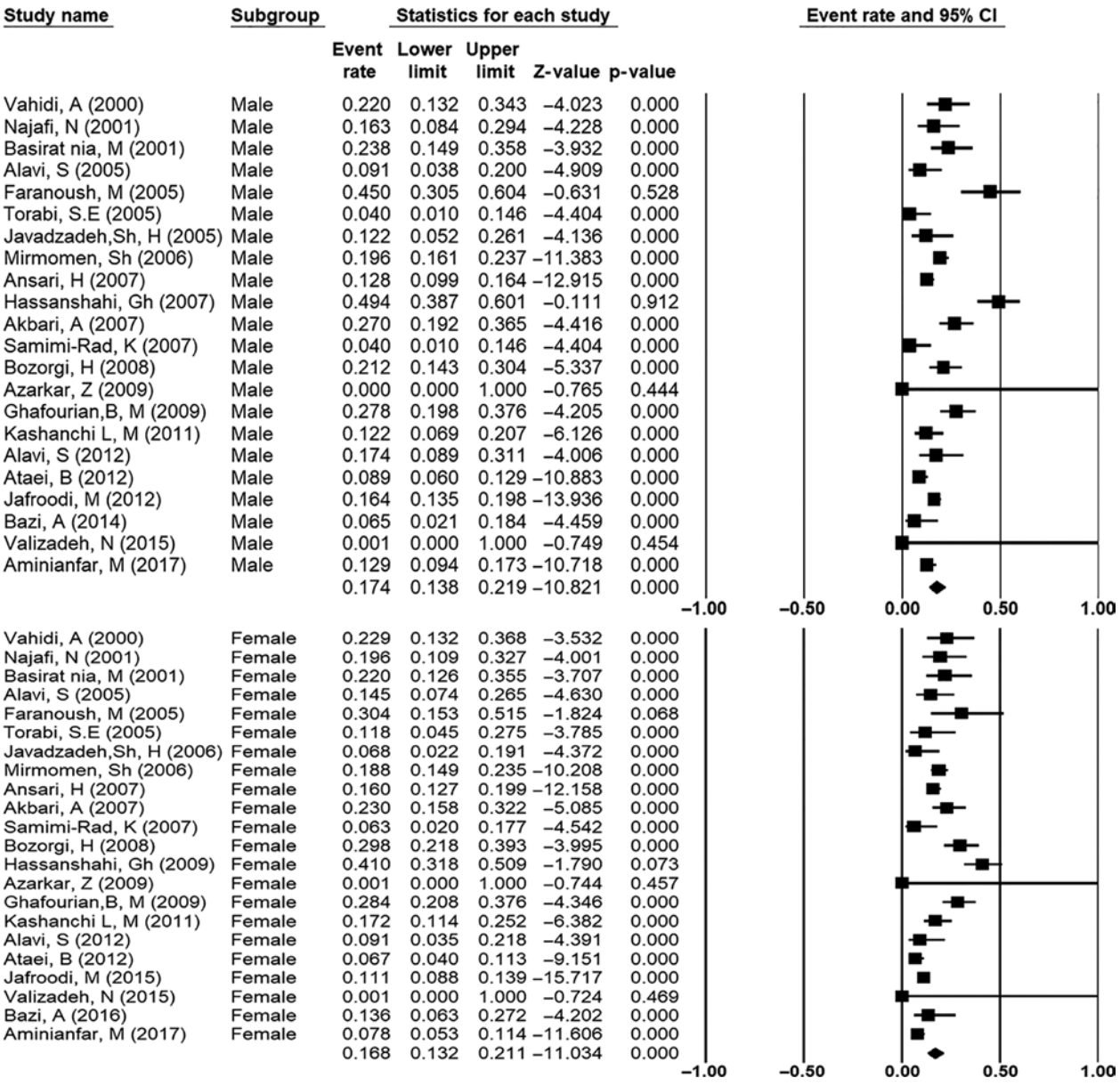

Figure 3: Forest plot of meta-analysis on the prevalence of hepatitis C infection among female and male patients with thalassemia in Iran with 95% CI.

Each horizontal bar shows the length of the confidence interval. The diamond at the end of the figure shows the pooled prevalence based on random-effects models.

or properly. Although thalassemia is an autosomal inherited disease and has no relationship with gender some studies have pointed to the relationship between gender and the incidence of the disorder, which may occur due to thalassemia and HCV, suggesting that being male gender increases the risk of developing the disease. Moreover, there are also some unconfirmed reports about the relationship between age and the rate of infection [64–66].

Studies conducted in Iran indicate a significant difference on the prevalence rate of HCV among thalassemia patients. So that the highest prevalence of 45.10% (95% CI; 33.0–57.6) was observed in the study of Arababadi et al. [38] in the Kerman Province and the study of Samimi-Rad and Shahbaz [36] in the Markazi Province with 5.1% prevalence being the lowest frequency (95% CI; 2.1–11.7). According to the meta-analysis carried out separately on different provinces with multiple studies HCV prevalence in the Kerman Province was 36.70% and in the Markazi Province was 6.20%. It seems that Kerman is one of the most prevalent provinces for thalassemia in Iran.

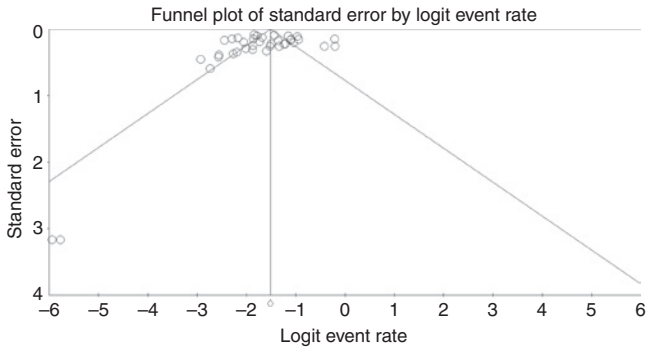

Figure 4: Funnel plot for publication bias.

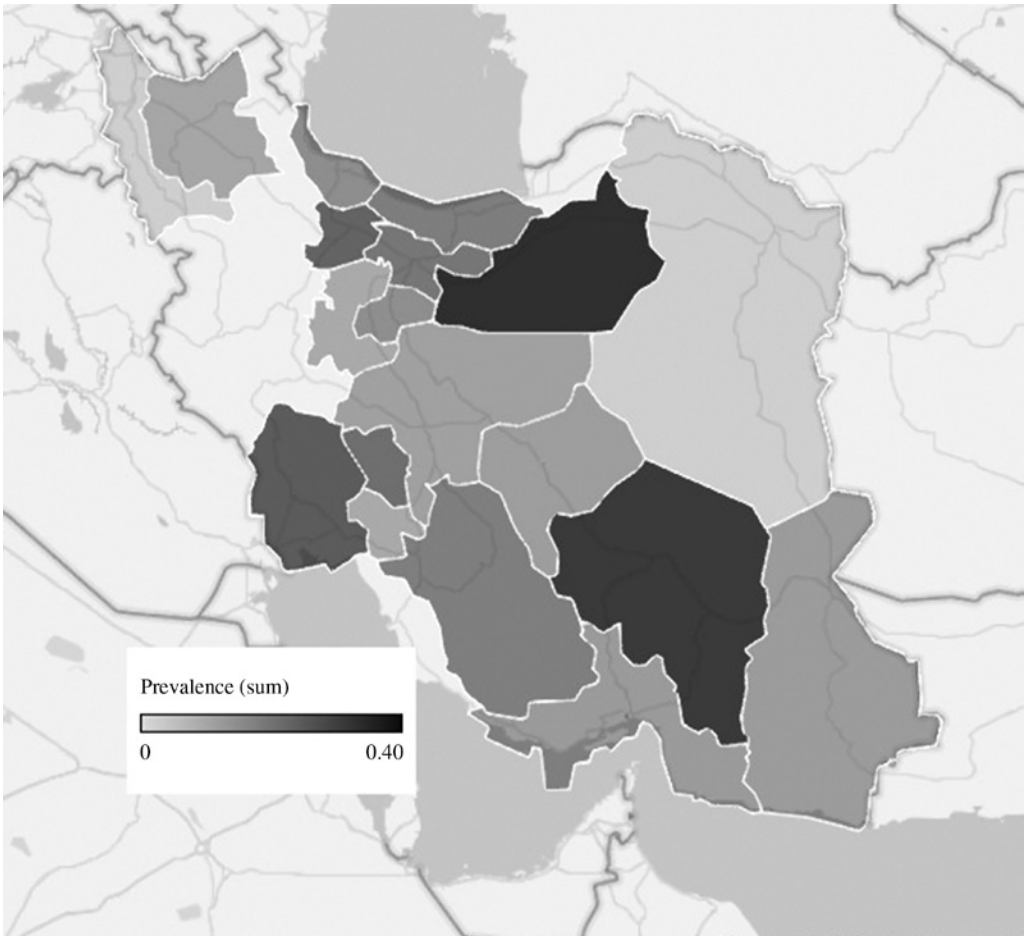

Figure 5: Distribution of HCV prevalence among patients with thalassemia in different regions of Iran.

Figure 6 shows that most provinces face a lack of comprehensive studies regarding the subject. Studies in 20 provinces on the prevalence of HCV among thalassemia patients was as follow: half of them have only one study, in 25% of the provinces, only two studies have been conducted and only in 25% of them, more than two studies were available. The trend line indicates the reduction of the prevalence from the first study to subsequent studies in most of the provinces with multiple studies. However, there are no regular changes in this trend. Certainly, this can be due to various reasons, such as sample size, year and duration of the study, the area of study and even the age and clinical features of patients under investigation. Indeed, the difference in the prevalence of HCV and risk

Region	1st Study	2nd Study	3rd Study	4th Study	5th Study	Total studies	Trend line
South Khorasan	0.00%					0.00%	
West Azerbaijan	0.00%					0.00%	
Kohgiluyeh and Boyer-Ahmad	6.10%					6.10%	
Markazi	5.10%	7.20%				6.20%	
East Azerbaijan	7.10%					7.10%	
Isfahan	9.10%	7.90%				8.60%	
Yazd	9.40%					9.40%	
Hormozgan	10.22%					10.22%	
Sistan and Baluchestan	13.46%	10.00%				12.80%	
Qom	13.40%					13.40%	
Gilan	13.60%					13.60%	
Mazandaran	18.00%	16.90%				17.60%	
Fars	15.70%	18.32%	14.40%	25.00%		17.70%	
Tehran	24.00%	11.80%	27.60%	13.30%		19.90%	
Chaharmahal and Bakhtiari	23.00%	21.00%				22.10%	
Khuzestan	26.20%	2.50%	28.15%			25.00%	
Qazvin	25.10%					25.10%	
Kerman	22.40%	45.10%	45.00%			36.70%	
Semnan	39.60%					39.60%	

Figure 6: Study trends in different provinces.

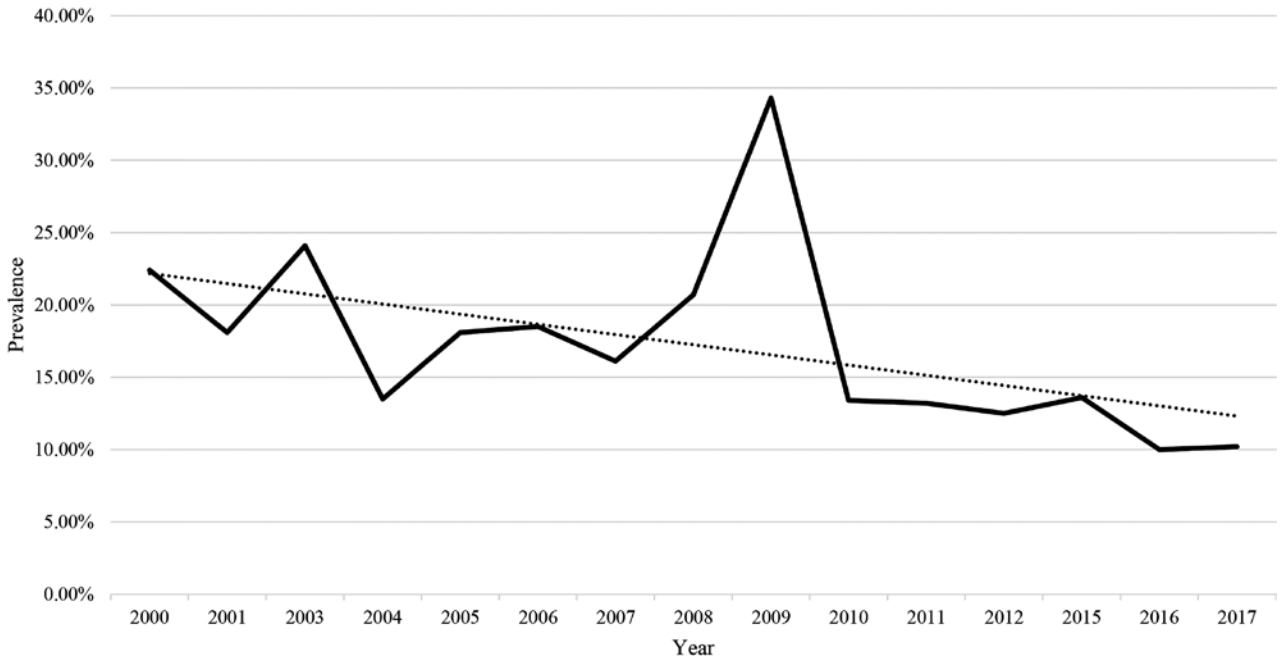

Figure 7: Trend of HCV prevalence among patients with thalassemia over time.

factors in the general population and blood donors may be the reason for the difference of heterogeneity in the geographical distribution of HCV in thalassemia patients [56].

By referring to the Figure 7, it is clear that the trend of HCV prevalence among patients with thalassemia has decreased over time. This decline certainly demonstrates

the good performance of diagnostic and therapeutic centers as well as timely screening programs of the blood transfusion organization of Iran that has prevented the disease from occurring.

As the purpose of this type of study is the regular and systematic review of available documents, the quantitative summarization, combination of the results of various studies, and providing a comprehensive interpretation of the results, therefore, present a general result from studies across Iran and is one of the remarkable points of present study, because there has been no recent comprehensive studies on this topic.

Limitations

This meta-analysis included several limitations, such as the failure to review abstracts of unpublished papers, papers presented at congresses, as well as the organizational reports, due to the inaccessibility and/or the lack of credibility. Besides, many epidemiological and scientific studies in Iran are conducted as dissertations and unfortunately, there is no comprehensive and coherent database at the national level for the systematic coverage and registration of these dissertations. In addition, it was not possible to evaluate the HCV trend in all the provinces of Iran. Moreover, this study cannot be completely generalized to the whole society of Iran, because in some parts (e.g. Ardabil, Bushehr, Golestan, etc.) there were no reports on the subject and in some provinces, only one study was conducted.

Conclusions

This meta-analysis has demonstrated the national prevalence of HCV among patients with thalassemia. Regarding the fact that, the prevalence rate declined over time, we can conclude that Iranian Blood Transfusion Organization has done a reasonably good job in screening blood donors for HCV infection.

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Author contributions: AS: study design, search strategy, data collection, data analysis, wrote and revised the primary and ending drafts of the full text. RA-N: The data analysis, reviewing of the manuscript. AAP: helped in the preparation and revising of the manuscript. RA: contributed to the writing of the primary draft and reviewed the manuscript. ARM: contributed to the writing of the primary draft, reviewed the manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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