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Hepatitis C virus prevalence among patients with thalassemia and inherited bleeding disorders in Iran: a systematic review and meta-analysis

Abstract

Background: Hepatitis C Virus (HCV) as the most common causes of post transfusion infections, is a major global health problem due to liver cirrhosis and hepatocarcinoma. HCV prevalence varies from each region of the world to another and is more prevalent in patients receiving blood transfusions. Hence, Patients with thalassemia and inherited bleeding disorders are at high risk of HCV infection. This systematic review and meta-analysis study aimed to determine Hepatitis C Virus prevalence among patients with thalassemia and inherited bleeding disorders in Iran.

Methods: Comprehensive searches were carried out in databases including PubMed, EMBASE, the Scientific Information Database (SID) of Iran, the World Health Organization Index Medicus for the Eastern Mediterranean Region (IMEMR WHO), Ebsco, Science Citation Index Expanded, Ovid, Google Scholar, Iran Medex and Magiran up to January 2017. The findings were reported following PRISMA guidelines. The pooled proportion rates were calculated using a Metaprop program on Stata version 14.1 for Mac. Also, the confidence intervals of each study were calculated using the exact method.

Results: Forty-seven studies, composed of 12449 patients; 8673 thalassemia and 3776 patients with inherited bleeding disorders (mainly hemophilia), fulfilled our criteria and included in the study. The year of data collected from the studies was between 1998 to 2015. The pooled HCV prevalence was estimated 28% generally (95% confidence intervals [CI]=22%-33%) and the HCV prevalence in patients with thalassemia and inherited bleeding disorders were 19% ([CI] 95%=16%-23%) and 42% ([CI] 95%=33%-52%), respectively. There was a considerable heterogeneity between studies.

Conclusion: Our findings indicated the high prevalence of HCV among patients with thalassemia and inherited bleeding disorders with a decreasing trend of past studies in Iran. Moreover, it is significantly higher in patients with inherited bleeding disorders than patients with thalassemia. In comparison with similar studies, the prevalence of HCV infection in Iran is low.

Keywords: Hepatitis C virus, Thalassemia, Inherited bleeding disorders, Iran, Systematic Review, Meta-Analysis

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Introduction

Among blood products transmitted viral infections, hepatitis C as the most important cause of post-transfusion complication corresponding to the 90% of post transfusion hepatitis.[1] Patients who require multi blood transfusion like patients with hereditary bleeding disorders and major thalassemia are noticeably at high risk of transfusion-transmitted infections.[2,3] Hepatitis C virus is a single-stranded RNA virus which is the main cause of non-A non-B hepatitis recognized in 1989.[4] HCV infection affected about 2-3% of the population and is a global health problem.[5] Clinically, it presents in two acute and chronic forms. Acute form is usually asymptomatic and rarely accompanies life-threatening conditions. Also, fifteen to forty-five percent of cases are treated within 6 months without any treatment. On the other hand 60% to 80% of subjects develop chronic form of disease which is a leading cause of liver cirrhosis within 20 years.[6] HCV as the main cause of chronic liver disease is responsible for the most hepatocellular carcinomas and requires intensive care.

Hereditary bleeding diseases (i.e. Hemophilia, Von Willebrand disease, clotting factors deficiency and etc.) are a group of conditions that result when the coagulation system doesn't function properly and patients experience extended bleeding after injury or even spontaneously. Thalassemia is a group of inherited disorders of the globin chain synthesis in which hemoglobin is reduced or absent. Thalassemia is classified based on the type of affected chain (alpha(α) or beta(β) thalassemia & ...). Major β-thalassemia reveals with a severe anemia about 6 months after birth and in the absence of treatment causes developmental disorder and skeletal malformation and ultimately reduces the patient's life. Therefore, regular blood transfusions are deemed necessary in these patients.[7]

Prior to 1990, almost all patients with hereditary coagulation disorders received HCV infected pooled plasma products.[2] Since 1990, screening tests have been available for Anti-HCV screening to reduce probability of transmission of this virus through the blood transfusions, but screening tests aren't able to detect virus during the window

period.[8] The transmission of viral infection by blood products depends on a variety of factors, including the prevalence of infection in the population, the prevalence of infection in donors, screening tests and vaccination status. Although vaccination against HBV and screening tests have played a greater role in controlling the HBV transmission, but HCV has already remained as a massive challenge and a major cause of post transfusion hepatitis in multi-transfused patients. This systematic review and meta-analysis study aimed to determine hepatitis C virus prevalence among patients with thalassemia and inherited bleeding disorders in Iran.

Materials and methods

Search strategy

The current meta-analysis study achieved by the "Preferred Reporting Items of Systematic Reviews and Meta-Analysis" PRISMA guidelines.[9] Following, biological and health sciences databases were searched: Pubmed, Scopus, EMBASE, Ebsco, Science Citation Index Expanded, Ovid, Google Scholar, Iran Medex, Magiran And Scientific Information Database (SID). The keywords were applied for search: "Viral Infection" OR "Hepatitis C" OR "HCV" AND "Prevalence" OR "Frequency" OR "Epidemiology" AND "Thalassemia" OR "Hemophilia" OR "Inherited Bleeding Disorders" OR "Multi-Transfused" OR "Blood Transfusion" AND "Iran". Moreover, reference lists of detected articles, reviews and meta-analysis were investigated for further eligible studies.

Inclusion and exclusion criteria

First, the titles and abstracts of the studies reviewed by tow trained researchers independently. The inclusion criteria were:

i. Studies surveying the HCV prevalence among Iranian provinces.

ii. Studies evaluated just Patients who receive blood products frequently.

iii. Studies used only validated diagnostic tests, including Polymerase Chain Reaction (PCR) and Recombinant Immunoblot Assay (RIBA) with the same Sensitivity and specificity.

iv. Studies written in English and Persian.

v. Observational studies like cross-sectional, case-control, prospective and retrospective.

The exclusion criteria were as follows: i) studies non-carried out among the Iranian population, ii) studies non-included enough data to assess the HCV prevalence, iii) studies used unvalidated diagnostic tests, including serological assays or Enzyme Linked Immunosorbent Assay (ELISA), iv) studies evaluating other risk factors of HCV transmission, v) identical and unrelated studies and vi) case-series, case reports, reviews, books, conference abstracts, editorial commentary. Afterward, the full text of the elected studies reviewed and observed contradictions resolved through discussion. Our research was performed from database inception up to January 2017.

Data extraction and quality assessment

The following retrieved study data were: title, first author name, year of publication, city of study, sample size and virus detection method. The quality of studies was evaluated using the Newcastle Ottawn Scale (NOS).[10] based on the scores, studies classified into three low, moderate and high-quality study with 0-3, 4-6 and 7-9 score, respectively.

Statistical analysis

We used Cochran Q and the I2 statistics to evaluate heterogeneity between the included studies ($I2=(Q–df)/Q\times100\%$; $I2< 25\%$, no heterogeneity; $I2=25–50\%$, moderate heterogeneity; $I2=50–75\%$, large heterogeneity, $I2>75\%$, extreme heterogeneity). Accordingly, heterogeneity was considered significant if the Q statistic had $p<0.1$ or $I2>50\%$. In the presence of significant heterogeneity, the random-effects model was applied; otherwise, the fixed-effect model was performed to combine the data.

The meta-analysis was performed using software version STATA 14.1. HCV prevalence with 95% confidence interval (CI) calculated by the Der Simonia-Laired random effects model.[11] I^2 test used to assess the heterogeneity among included articles.[12] A sensitivity analysis carried out to assess the stability of the results and Egger's regression test used to evaluate publication bias. A P-value less than 0.05 considered statically significant.

Results

Forty-seven studies, composed of 12449 patients; 8673 thalassemia and 3776 patients with inherited bleeding disorders (mainly hemophilia), fulfilled our criteria and included in the meta-analysis. The year of data collection in the studies were between 1998 to 2015 (Table 1).

The pooled HCV prevalence was estimated 28% (95% confidence intervals [CI]=22%-33%). The prevalence in patients with thalassemia and inherited bleeding disorders were 19% ([CI] 95%=16%-23%) and 42%([CI] 95%=33%-52%), respectively (Figure 1). There was a considerable heterogeneity between studies. The highest prevalence of HCV infection (54%) in patients with bleeding disorders was observed in the Tehran province and the lowest rate (6%) in West Azerbaijan province (Figure 2). The prevalence trend of HCV in the patients assessed from 2000 to 2012 years. The findings of this assessment showed that the prevalence varies from year to year, but the trend was not logical (Figure 3).

Table 1 Summary of included studies

Author	Year	Region	SS	Disease	HCVpos	Method	Quality of study
Samimi-Rad	2006	Yazd	77	bleeding disorders	41	RIBA	high
Samimi-Rad	2006	Yazd	93	Thalassemia	11	RIBA	high
Tamaddoni,	2006	Babol	113	Thalassemia	12	ELISA	Medium
Kalantari	2010	Isfahan	545	Thalassemia	31	RNA	high
Kalantari	2010	Isfahan	615	bleeding disorders	347	RNA	high

Table Continued..

Author	Year	Region	SS	Disease	HCVpos	Method	Quality of study
Shari -Mood,	2006	Zahedan	81	bleeding disorders	24	RIBA	High
Jafroodi	2012	Guilan	1113	Thalassemia	151	RIBA	High
Assarehzadegan	2009	Khuzestan	87	bleeding disorders	42	RNA	High
Valizadeh	2010	West Azarbaijan	50	bleeding disorders	3	RIBA	High
Ansar	1998	Rasht	67	Thalassemia	50	RIBA	High
Hassanshahi	2011	Southeastern	181	Thalassemia	81	RNA	High
Azarkeivan	2011	Tehran	395	Thalassemia	109	RIBA	High
Yazdani	2010	Isfahan	350	bleeding disorders	232	RIBA	High
Sanei moghdam	2003	Zahedan	364	Thalassemia	49	RIBA	High
Torabi	2003	East Azarbaijan	84	Thalassemia	6	RIBA	High
Shahshahani	2003	Yazd	85	Thalassemia	8	RIBA	High
Shahshahani	2003	Yazd	74	bleeding disorders	36	RIBA	High
Azarkeivan	2010	Tehran	395	Thalassemia	109	RIBA	High
Pedram	2006	Ahvaz	634	Thalassemia			
Kasraian	2011	Isfahan	570	Thalassemia	60	RIBA	High
Kasraian	2011	Isfahan	350	bleeding disorders	232	RIBA	High
Karimi	2001	Shiraz	466	Thalassemia	73	RIBA	High
Karimi	2001	Shiraz	755	Thalassemia			
Mirmomen	2006	Multicenteric	732	Thalassemia	141	RIBA	High
Sayad	2015	Kermanshah	232	Thalassemia	14	RIBA	High
Kazemi Arababadi	2008	Kerman	60	Thalassemia	27	RNA	high
Alavian	2003	Qazvin	103	Thalassemia	23	RIBA	High
Mahdaviani	2004	Markazi	97	Thalassemia	7	RIBA	High
Mahdaviani	2004	Markazi	68	bleeding disorders	25	RIBA	High
Akbari	2004	Shiraz	200	Thalassemia	50	RIBA	High
Alavi	2002	Tehran	110	Thalassemia	11	RNA	High
Alizadeh	2006	Hamedan	66	bleeding disorders	28	RNA	High
Boroujerdnia	2007	Khuzestan	206	Thalassemia	46	RNA	High
Bozorg	2005	Qazvin	207	Thalassemia	50	RIBA	High
Esfahani	2012	Hamedan	77	bleeding disorders	15	RNA	High
Faranoush	2002	Semnan, Damghan, Garmsar	63	Thalassemia	12	RNA	High
Keshvari	2014	Tehran	257	Thalassemia	103	ELISA	Medium
Kashanchi Langarodi	2010	Karaj	206	Thalassemia	29	RIBA	High
Mobini	2006	Yazd	77	bleeding disorders	38	RIBA	High
Mousavian	2006	Tehran	1095	bleeding disorders	593	RNA	High
Maziar Mojtabavi	2006	Isfahan	553	bleeding disorders	125	RNA	High
Najafi	1998	Ghaem Shahr	100	Thalassemia	18	ELISA	Medium
Sammak	2007	Qom	142	Thalassemia	19	RIBA	High
Samimi-Rad	2007	Markazi	98	Thalassemia	5	RNA	High
Samimi-Rad	2007	Markazi	76	bleeding disorders	33	RNA	High
Ziaee	2000	Khorasan	80	bleeding disorders	25	RNA	High

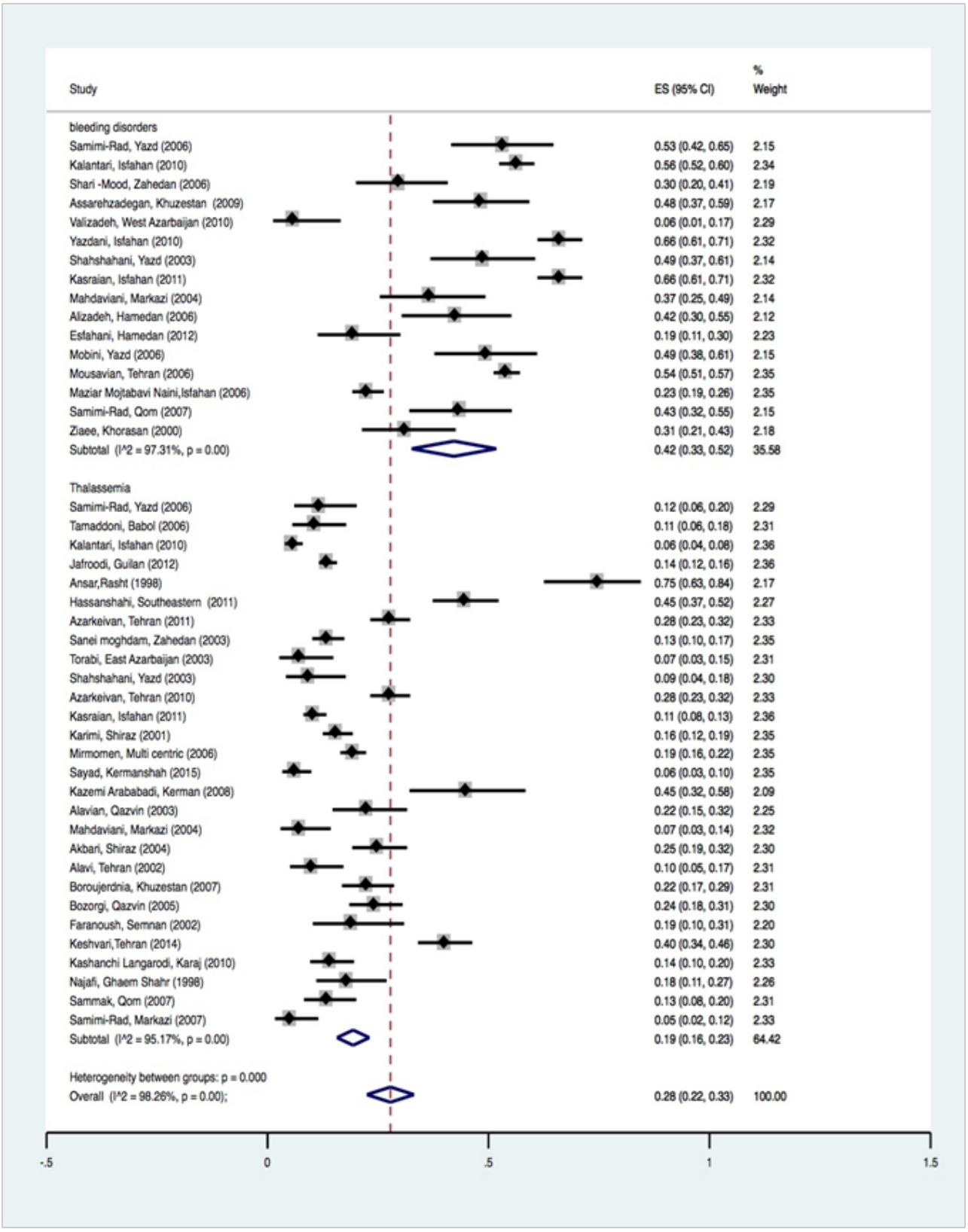

Figure 1 Prevalence of HCV in multi transfused patients.

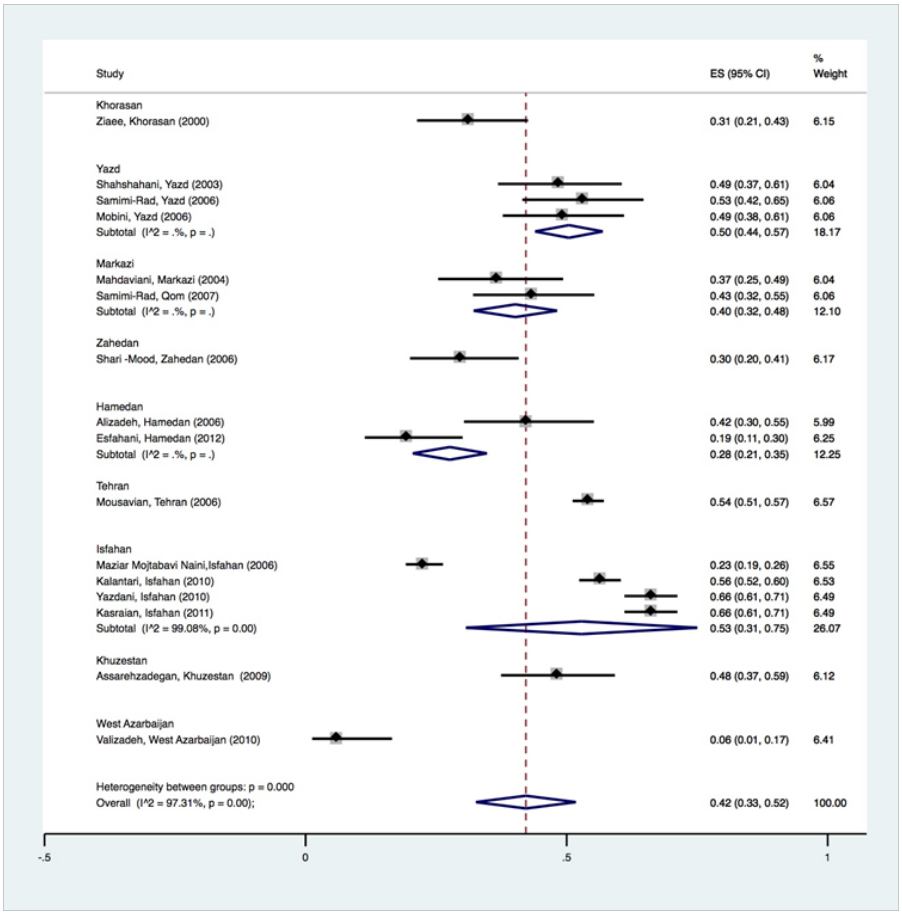

Figure 2 Prevalence of HCV in patients with bleeding disorders subgrouping by region.

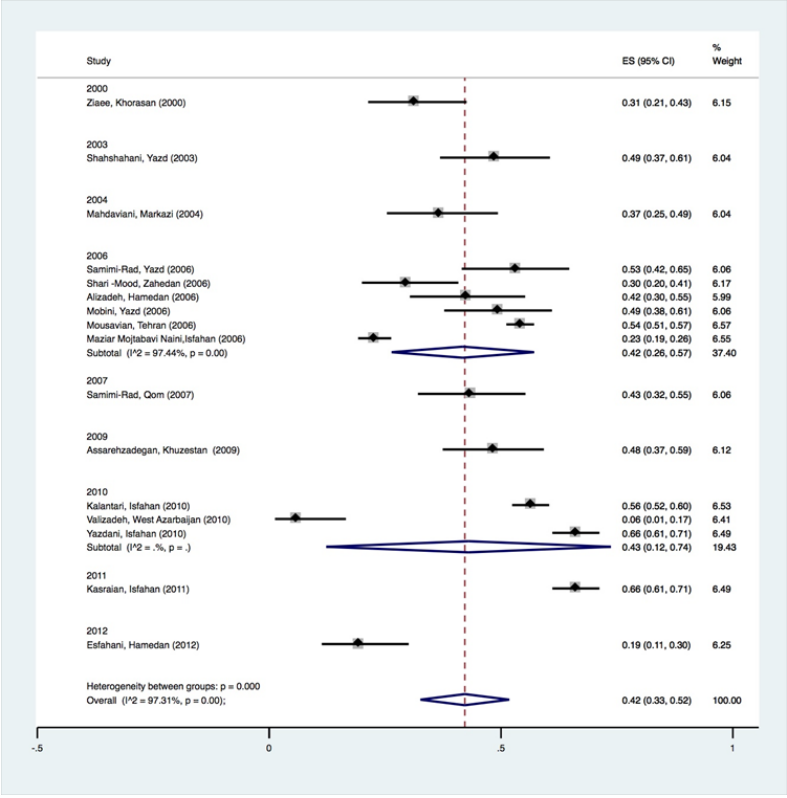

Figure 3 Prevalence of HCV in patients with bleeding disorders subgrouping by study year.

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Discussion

Todays, most HCV infected patients have used common needles or other injection equipments or because of the multi-transfused disease like thalassemia and hereditary bleeding disorders (HBD) were at high risk of HCV infection transmission through the blood transfusions. It is confirmed by a study in Iran; that the HCV subtypes distribution in patients with HBD was different from intravenous drug users (IDUs) patients and similar to patients requiring multi blood transfusion like thalassemia and dialysis patients.[13]

In this study, the prevalence of HCV infection in patients with thalassemia and HBD (mainly hemophilia) was 19% and 42%, respectively. Studies in different regions of the world, depending on the method and time, have presented several statistics on the incidence of HCV among the patients with multi-transfusions. For instance, in Scotland patients with HBD that were infected with HCV due to the pooled plasma were estimated about 455 people, between 1970-1989.[14] In another study in Bosnia, about 38.7% of patients with hemophilia had HCV infection. Also, in the Netherlands, about 68% and in the United States until 1993, 89% of hemophilia patients became infected by HCV infection due to receiving polluted coagulation factor concentrate.[2] In Iran, the statistic of hemophilia patients based on the positive anti-HCV test ranged from 15.6% to 76.7% and it was estimated at about 40.8% in a meta-analysis study.[15] Only about 20% of these patients recover spontaneously and chronic HCV infection is a serious problem for this group of patients and its mortality is 10 times higher than general population mainly due to Hepatic cirrhosis and hepatocarcinoma.[2]

Thalassemia patients need regular blood transfusion to treat anemia. Prevalence of HCV infection in older patients (with higher ferritin level and reflecting higher blood transfusions) confirms the role of healthy blood supply to reduce HCV infection in the thalassemia population.[16] In our meta-analysis, the prevalence of HCV in patients with thalassemia was about 19%. As the findings show there was a considerable heterogeneity between the studies and the prevalence varies from each region to another (Table 1). The prevalence of HCV among the thalassemia patients in Iran has been reported in various studies between 7.1% in East Azerbaijan and 55.5% in Kerman.[3] This heterogeneity may be due to the different number of patients in each study and different years of studies. Also, some provinces didn't study multi-transfused patients, recently. In a study conducted on thalassemia patients using the Elisa method in 5 provinces (Tehran, Kerman, Qazvin, Zanjan and Semnan), the prevalence of HCV infection was 19.6%.[2] Alavian et al.[15] studied the prevalence of HCV infection in β-thalassemia patients in Eastern Mediterranean Countries using enzyme immunoassay for testing anti-HCV antibody. It was 18% (95% CI 14-21), 45% (95% CI 43-48), 63% (95% CI 56-69) and 69% (95% CI 58- 80) in Iran, Pakistan, Saudi Arabia and Egypt, respectively. Also, the infection in patients who had received blood before 1996 was 7.6 times higher than those who received blood after 1996.[16] This was due to the lack of screening of blood donors before 1996, and this is the main cause of the high prevalence of HCV in patients with multi-transfusion.[17] In a study published in 2015 by Jafroodi et al.[18] the prevalence of hepatitis in thalassemia patients using RIBA and ELISA methods during 10 years reported 13.6%.[18] Other studies in Asian countries reported the HCV prevalence in thalassemia patients 13.5%, 51% and 20% in Iraq, Oman and Egypt respectively.[19-21] Also in Thailand this prevalence was 14% in children and 32% in adults.[22] Concerning the Arab countries, it has been reported to be 33% in Kuwait and 40% in Bahrain and Jordan and 51% in Oman.[16,20] Due to the blood transfusion is an important risk factor for HCV infection among the multi-transfusion patients, accurate screening of donors is very effective to prevent the transmission of viral infections.

After using the 3rd Generation ELISA kits in IBTO (Iranian Blood Transfusion Organization) for detection of anti-HCV, the prevalence of HCV among the multi-transfusion patients reduced significantly. In a study conducted by Mirmomen and colleagues (2006), the prevalence of HCV infection in β-thalassemia patients ranged from 22.8% before the screening, to 2.6% after the screening of donated bloods.[16] Given that multi-transfusion patients are exposed to blood-borne infections during their life, using advanced screening techniques on donated blood plays an important role in preventing the transmission of infection. Also, regular monitoring of the patients would be helped with early detection of the transmitted infections in these patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

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