Iranian Red Crescent Medical Journal

ORIGINAL ARTICLE

Epidemiology of HCV Infection among Thalassemia Patients in Eastern Mediterranean Countries: a Quantitative Review of Literature

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Abstract

Background: Hepatitis C infection (HCV) is the major co-morbidity in thalassemia patients; however, literature lacks data from many EMRO counties. There is also enormous heterogeneity in the available study results in this region, and distribution of HCV infection among these patients living in this region is still unknown. This study provides a comprehensive and reliable tabulation of available data on the epidemiological characteristics and risk factors for hepatitis C virus (HCV) infection in thalassemia patients in eastern mediterranean countries.

Methods: A systematic review was carried out based on the computerized literature database. 95% confidence intervals of infection rates were calculated using the approximate normal distribution model. Pooled Odds ratios and 95% CI were calculated by fixed or random effects models. The heterogeneity was assessed by either Q or χ^2 statistics. Publication bias was evaluated by either Harbor's modified or Egger's test.

Results: We identified 40 studies that fulfilled our inclusion criteria involving 8554 thalassemia subjects. Pooled HCV seroprevalence 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. Among Iranian thalassemia patients, splenectomy OR=4.1 (95% CI 1.5-11.2), high transfusion OR=3.5 (95% CI 1.8-7), high age OR=6.1(95% CI 1.2-31.2) and first transfusion before 1996 OR=7.6 (95% CI 4.7 -12.3) were major risk factors of HCV infection.

Conclusions: There are no data from many EMRO countries. Among major EMRO countries, Iran has the least seroprevalence of HCV infection among thalassemia patients. This underscores more advanced blood safety in this country compared with other countries with comparable population in this region.

Keywords: Systematic review; Meta-analysis; Thalassemia; HCV; EMRO; Iran

Introduction

Hepatitis C virus (HCV) infection is a major, worldwide health problem.[1] It is estimated that over 170-200 million people are infected and the virus is distributed worldwide with a prevalence varying in different countries from 0.2 up to 40%.[2,3] While rigorous donor screening, testing procedures and suitable donor selection programs have dramatically reduced transmission of HCV via transfusion of blood products, there are still many countries where standards of blood product management do not adequately protect chronically-transfused patients especially thalassemia patients from this complication.[4-6] Up to 80% of the adult thalassemia patients are infected with HCV infection in the world,[7] but there is tremendous discrepancy between epidemiological studies intra- and inter- countries in Eastern Mediterranean region. For example, in Iran HCV infection rate ranges from 2 to 32% and in Saudi Arabia from 33 to 93%. Most of these studies also suffer inadequate sample size. In some countries such as Egypt and Jordan, the publication date of available data backs to one or two decades ago and updated data are not available. All

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Received: April 22, 2010 Accepted: June 7, 2010

together, to find gaps in our current epidemiological knowledge and to understand hepatitis C virus infection in thalassemia patients in this region, we tried systematically to collect all respective epidemiological studies conducted in EMRO countries and apply the quantitative methods of meta-analysis to estimate the distribution of HCV infected thalassemia patients in the region.

Materials and Methods

We carried out an electronic search on seroepidemiology of Hepatitis C virus infection in thalassemia patients in the EMRO countries on MEDLINE, SCOPUS, EMBASE/Excerpta Medica, Google Scholar (for Local websites and medical journals), OVID and ISI without temporal limits by different combinations of the following keywords: ''thalassemia'', 'hepatitis C virus' or 'HCV' or 'chronic hepatitis C'. The Eastern Mediterranean countries that were added to our search strategy were as following: Iran, Iraq, Afghanistan, Pakistan, Bahrain, Kuwait, Jordan, Lebanon, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, United Arab Emirate, Yemen, West bank, Egypt, Libyan Arab Jamahiriya, Djibouti, Morocco, Somalia, Sudan, Tunisia. Persian-specific databases including SID, EMR Medex, websites of Iranian universities, Iran Medex and MagIran were searched using aforementioned keywords. The PakMediNet was accessed and 58 indexed journals were browsed for relevant epidemiological studies. The websites of regional journals from WHO-EMRO indexing site were also searched. Citations in the retrieved papers were reviewed to find further published studies.

A single investigator reviewed all the potentially relevant papers. Studies published in English, Persian and French and Arabic were eligible if they fulfilled the following criteria: (1) study design: cohort, case control, cross-sectional; (2) sample origin: thalassemia patients (3) studies using enzyme immunoassay for testing anti-HCV antibody (4) studies reporting anti-HCV antibody positive rates among patients in the Eastern Mediterranean countries. Exclusion criteria were as follows: (1) studies presenting confusing data or probable errors (2) studies that included subjects with symptomatic liver disease or elevated liver enzymes. If there was any uncertainty, it was settled by consensus. The data were abstracted with standardized data-abstraction forms. The following information was sought from each eligible study: first author's name; year of publication; journal; country of sample's origin; type of study (cohort, case control or cross-sectional); sample size; and RIBA, and some study population characteristics including the mean age and proportion of male subjects from total sample size were extracted if full-text of the reports were available.

The 95% CIs of the seroprevalence of anti-HCV antibody among thalassemia patients for each of the included studies were computed using the approximate normal distribution model. The pooled estimate of anti-HCV Ab seropositivity rates accompanied by 95% CIs for each country was computed if there was more than one study. For Iranian studies, random effects model of DerSimonian and Laird was used to calculate the pooled infection rate. The random effects model provides a more conservative estimate of significance. This model operates under the assumption that the included studies are only a random sample of all studies that will be conducted so that heterogeneity among individual studies will result in a wider CI of the summary estimate. Therefore, using the DerSimonian and Laird random effects model, the reported summary estimate was calculated as an average of the individual study results weighted by the inverse of their variances (variance for each study is the sum of the variance within studies plus the variance between studies).[8] Because there were significant heterogeneity in different studies from Iranian provinces and other EMRO countries as well as the low number of studies and subjects, random effects model could result in a wide range of HCV serostatus estimate; thus, to reach a meaningful estimate of infection rate in Iranian provinces and other EMRO countries, we applied a fixed effect model of inverse variance. Under the fixed-effect model it is assumed that there is one true estimate which underlies all the studies in the analysis, and that all differences in the observed results are due to sampling error (variance between studies are assumed zero). In this model, summary estimate is an average of the individual study results weighted by the inverse of their within study variances that results in tighter CI for summary estimate. Furthermore, because in this model the lower weight is put on the smaller studies than random effects model, its summary estimate becomes less affected by the presence of publication bias. The estimate of heterogeneity was taken from the Mantel-Haenszel model for odds ratios of reported risk factors; under the null hypothesis of the test of heterogeneity, there is no difference in

treatment effect between groups (this follows a χ^2 distribution with k-1 degree of freedom, where k is the number of studies contributing to the meta-analysis. Heterogeneity estimation for HCV infection rates was made using Q statistic under the same null hypothesis. Study results were considered heterogeneous if the resultant P-value was less than 0.1.[9] I^2 was also used to provide a measure of the degree of inconsistency in the studies' results. Its quantity, describes the percentage of the total variation across studies that is due to heterogeneity rather than chance. I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.[10] Publication bias assessment was carried out using Harbord's modified test for ORs and Egger test for single group summary estimate of infection rates. The publication bias was considered significant if the resultant P value was less than 0.1. The Egger test performs a linear regression of the estimates on their standard errors, weighting by 1/ (variance of the estimate). This test is recommended for effects measured as mean differences or single group summary estimate but can suffer from false-positive test results when analyzing odds ratios because of the mathematical association between the log odds-ratio and its standard error.[11-13] Therefore, Harbord's modified test was employed to evaluate publication bias for summary estimate of ORs. The Harbord test regresses Z/sqrt(V) against sqrt(V), where Z is the efficient score and V is Fisher's information (the variance of Z under the null hypothesis).[14] Data manipulation and statistical analyses were undertaken using STATA 8.0 (STATA Corporation, College Station, TX, 2003).

Results

Based on the data provided in titles and abstracts, we retrieved 45 relevant citations that evaluated anti-HCV antibody serostatus in thalassemia patients from EMRO countries. All the studies were carefully examined to avoid including duplicate papers; 2 studies with duplicate data of the same patients were excluded.[15,16] One study from Pakistan was excluded because it did not use ELISA for screening of anti-HCV antibody.[17] No data were available from the following countries: Djibouti, Morocco, Somalia, Sudan, Syria, Emirate, Oman, Qatar, Yemen, West Bank and Afghanistan. We found three citations that were not available online and despite contacting their authors or publishers we could not obtain their abstracts.[18-20] We found 21 studies involving 5229 subjects from Iran, 8 studies including 1371 subjects from Pakistan, and 3 and 2 studies with 138 and 42 subjects from Saudi Arabia and Egypt, respectively. Only 1 study was identified from Bahrain, Iraq, Kuwait, Jordan, Lebanon and Libya. In the studies from Iran, 15 involving 3371 subjects confirmed positive ELISA with RIBA test. Ten studies (2426 subjects) and another 10 (2698 subjects) also used the 2nd and 3rd generation of ELISA, respectively. The mean age of the subjects ranged from 9.7 to 22.4 years. Gender distribution ranged from 43% to 61% male. Seven studies included all thalassemia patients in the city and nearby region (Census sampling, Table 1). 7 studies had case-control (C-C) design and the other 14 ones were simple cross-sectional (C-S) studies (Table 1).

Summary Estimate of HCV Infection and Risk Factors in Iranian Thalassemia Patients

In Iran from a total of 5229 thalassemia subjects, 941 (17.9%) were anti-HCV antibody positive. In 568 cases, positive ELISA was confirmed by RIBA test. The pooled estimate of positive anti-HCV serostatus in Iran was 18% (95% CI 14-21 Q(23)=220.5, p<0.0001, tau-squared=0.005, I-squared=89% in DerSimonian & Laird method and 15% (95% CI 14-16%) in fixed effect model with inverse variance method. Figure 1 shows the geographical distribution of HCV infection among Iranian thalassemia patients. Publication bias assessment was at the borderline of statistical significance (p=0.09). Pooled and individual estimation of HCV seroprevalence according to the provinces where the studies are conducted in is presented in Figure and Table 1. Its seroepidemiology ranged from 2 to 32%. Table 2 represents pooled ORs for risk factors of HCV infection in Iranian thalassemia patients together with their heterogeneity and publication bias assessments. OR for the likelihood of positive serology for HCV infection was 28.9 (95% CI 18.9-44) in thalassemia patients compared with general population; however, this OR was 11.94 (95% CI 8.40-16.98) for hemophilia compared with thalassemia patients.

Summary Estimate of HCV Infection in Thalassemia Patients from Other Eastern Mediterranean Countries

Table 3 shows the studies from other EMRO countries. Pooled HCV infection rate was 45% (95% CI 43-48) in Pakistan (640/1406), 63% (95% CI 56-69) in Saudi Arabia (71/138) and 69% (95% CI 58-80)

Table 1: The study and patients' characteristics from Iran

Ref. No.	Author	Publication year	Design	Provinces	Sample size	ELISA	RIBA	Mean age	Male (%)	Prevalence (%) 95% CI
15	Alavian et al.[15]	2003	Census (C-C)	Qazvin	95	2nd	Yes	12±7	48	24 (15-33)
27	Mirmomen et al.[27]	2001	C-S	Tehran	410	2nd	No	22.4± 7.8	61	27 (23-31)
28	Alavi et al.[28]	2005	C-S	Tehran	110	2nd	Yes	11.5±5.2	50	11 (5-17)
5	Mirmomen et al.[5]	2006	C-S	Tehran Zanjan Qazvin Semnan Kerman	732	3rd	Yes	17.9± 9.0	56	19 (17-22)
(29)	Bozorghi et al.[29]	2008	Census (C-S)	Qazvin	207	3rd	Yes	14.29±6.5	50	26 (20-32)
(30)	Kompani et al.[30]	2008	C-S	Khuzestan	195	2nd	No	14.9±6	50	21 (15-27)
(31)	Ghafourian et al.[31]	2009	C-S	Khuzestan	206	3rd	No	16.4±6.42	47	28 (23-33)
(32)	Tamaddoni et al.[32]	2007	C-S	Mazandaran	113	3rd	No	15.8±8.93	43	11 (5-17)
(33)	Ameli et al.[33]	2008	C-S	Mazandaran	65	3rd	No	19.5±8.9	NR	17 (10-24)
(34)	Shariatzadeh et al.[34]	2000	C-C	Markazi	54	2nd	Yes	Range (1-36)	NR	9 (1-17)
(23)	Samimi-Rad et al.[23]	2007	C-C	Markazi	98	3rd	Yes	12.4	51	5 (1-9)
(35)	Mahdaviani et al.[35]	2008	Census (C-C)	Markazi	97	3rd	Yes	13.1±7.3	51	7 (2-12)
(36)	Ansari et al.[36]	2007	C-S	Fars	806	2nd	No	15.3±6.82	50	14 (12-16)
(37)	Akbari et al.[37]	2007	C-C	Fars	200	2nd	Yes	15.2±6.3	50	25 (19-31)
(38)	Karimi et al.[38]	2001	C-S	Fars	466	2nd	Yes	12.3 ± 5.0	52	16 (13–19)
(39)	Kadivar et al.[39]	2001	C-S	Fars	147	2nd	Yes	13.6±4.8	55	27 (20-34)
(40)	Javadzadeh-Shahshahani et al.[40]	2006	Census (C-C)	Yazd	85	2nd	Yes	12.6±7.56	48	9 (3-16)
(41)	Hariri et al.[41]	2006	Census (C-S)	Isfahan	616	3rd	Yes	15.5±8	NR	11 (8-12)
(42)	Faranoush et al.[42]	2006	Census (C-S)	Semnan	63	2nd	No	11.8±4.7	60	40 (28-52)
(24)	Zahedi et al.[24]	2003	Census (C-C)	Kerman	100	2nd	Yes	11.5±5.7	45	31 (24-38)
(43)	Sanei-Moghaddam et al.[43]	2004	C-S	Sistan and Baluchistan	364	2nd	Yes	9.7±5.2	57	13 (10-16)

in Egypt (42/63). Publication bias was non-significant for meta-analysis of the studies from Pakistan (p=0.7) and Saudi Arabia (p=0.8). Infection rate among thalassemia patients in the countries for which only one report was available ranged from 11 and 14% in Libya and Lebanon to 65% in Iraq. Pooled or individual estimation of HCV seroprevalence in these countries are presented in Figure 7.

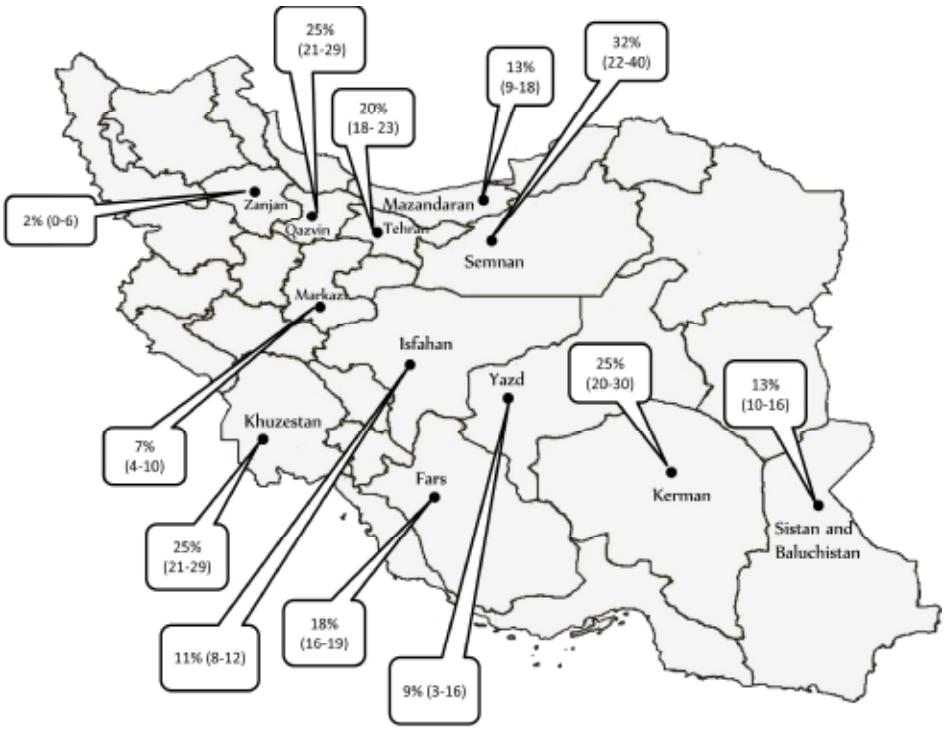

Fig. 1: Regional distribution of pooled or individual prevalence of hepatitis C virus infection among thalassemia patients in Iran

Table 2: Pooled estimation of ORs with 95% confidence interval for risk factors of HCV infection in thalassemia patients reported in the studies from Iran. Comparison with Iranian general population and hemophilia patients is also provided herein

Risk factors	No. of subjects	No. of studies	Model*	Pooled OR 95% CI	Harbord's *P* value**	Failsafe N.***	Heterogeneity assessment			
							χ^2	*P*	I^2 (%)	$\leftarrow^2$****
Thalassemia vs. general population (Figure 2)	8445	2	Fixed	28.9 (18.9-44)			0.6	0.4	0	0
Thalassemia vs. hemophilia	1234	4	Fixed	0.08 (0.06-0.12)	0.02		2.3	0.5	0	0
Transfusion before 1996 (Figure 3)	1778	9	Fixed	7.6 (4.7-12.3)	0.09	118	9.1	0.3	12	0.1
Splenectomy (Figure 4)	475	4	Random	4.1 (1.5-11.2)	0.2	17	9.2	0.02	67	0.6
High age (Figure 5)	761	5	Random	6.2 (1.2-32.1)	0.5	10	19.5	0.001	74	2.4
High transfusion number (Figure 6)	573	5	Random	3.5 (1.8-7)	0.1	13	2.6	0.6	0	0

*fixed effect model was carried out according to Mantel and Haenszel method and random effects model using DerSimonian & Laird method. **small study effect assessment was conducted according to Harbord's modified test. ***file-drawer analysis. Failsafe N. is a number of void or negative trials that can render meta-analysis meaningless. ****between study variance.

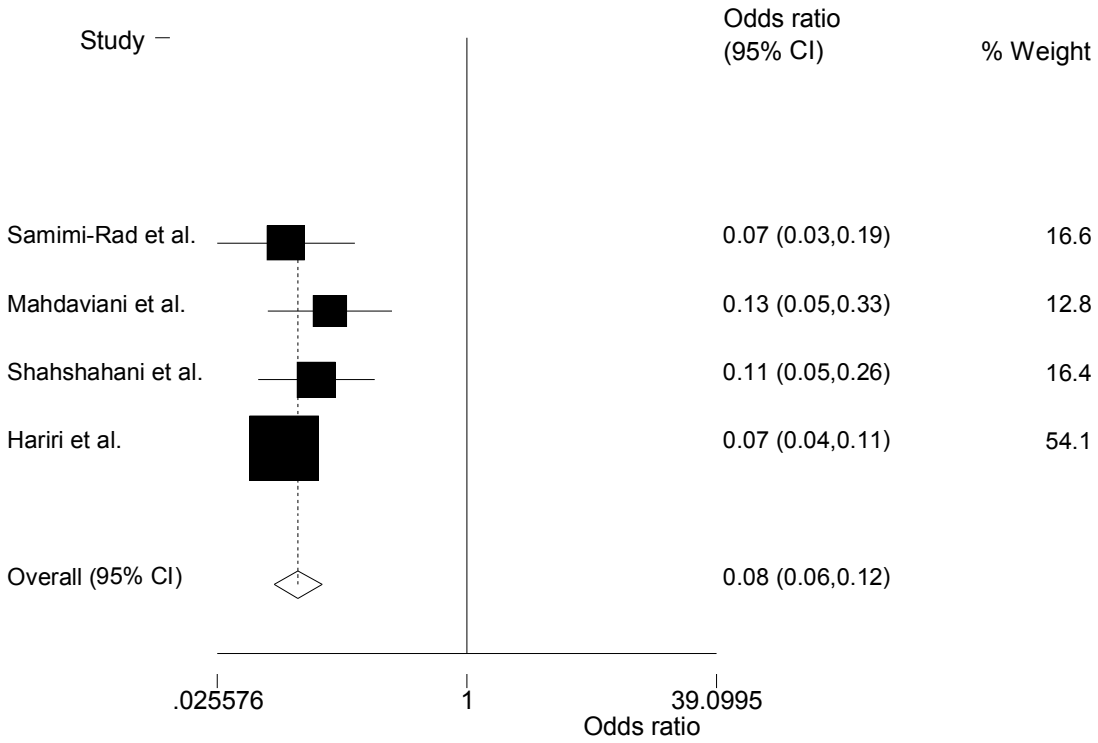

Fig. 2: Estimate of ORs with 95% confidence interval for positive HCV serostatus in Iranian thalassemia versus hemophilia patients

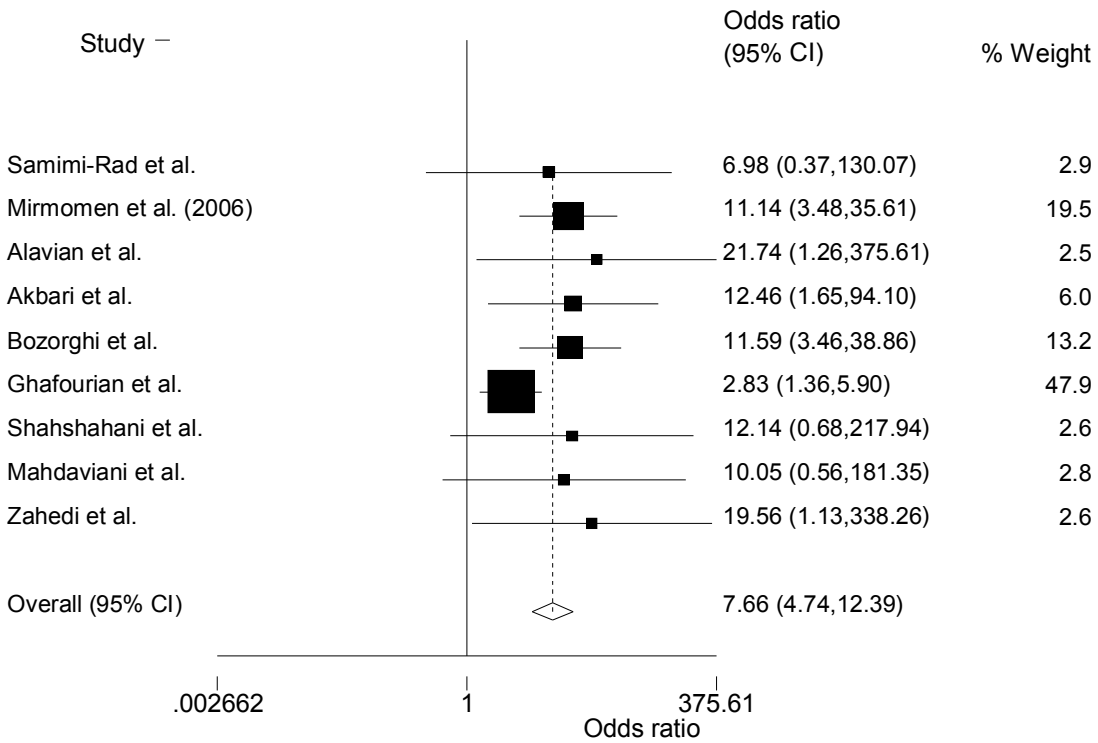

Fig. 3: The estimate of ORs with 95% confidence interval for positive HCV serostatus in Iranian thalassemia patients who received their first transfusion before 1997 versus patients who received their first transfusion after 1997

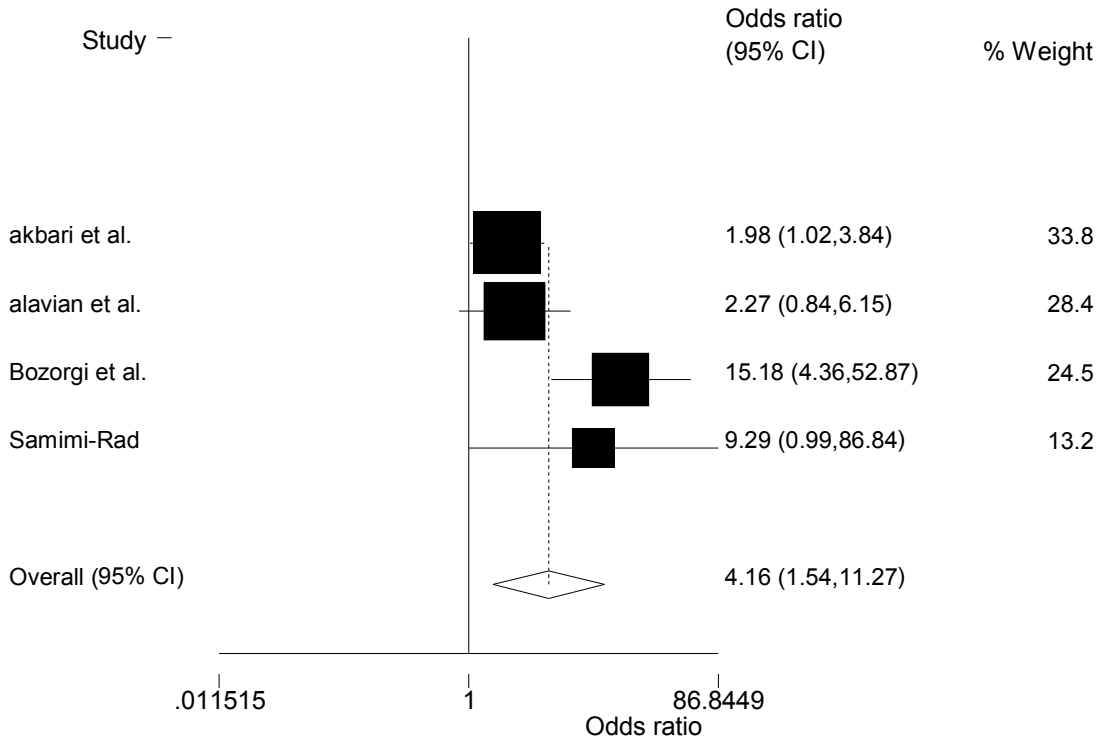

Fig. 4: Summary estimate of ORs with 95% confidence interval for positive HCV serostatus in Iranian thalassemia patients with a history of splenectomy versus those who did not undergo splenectomy

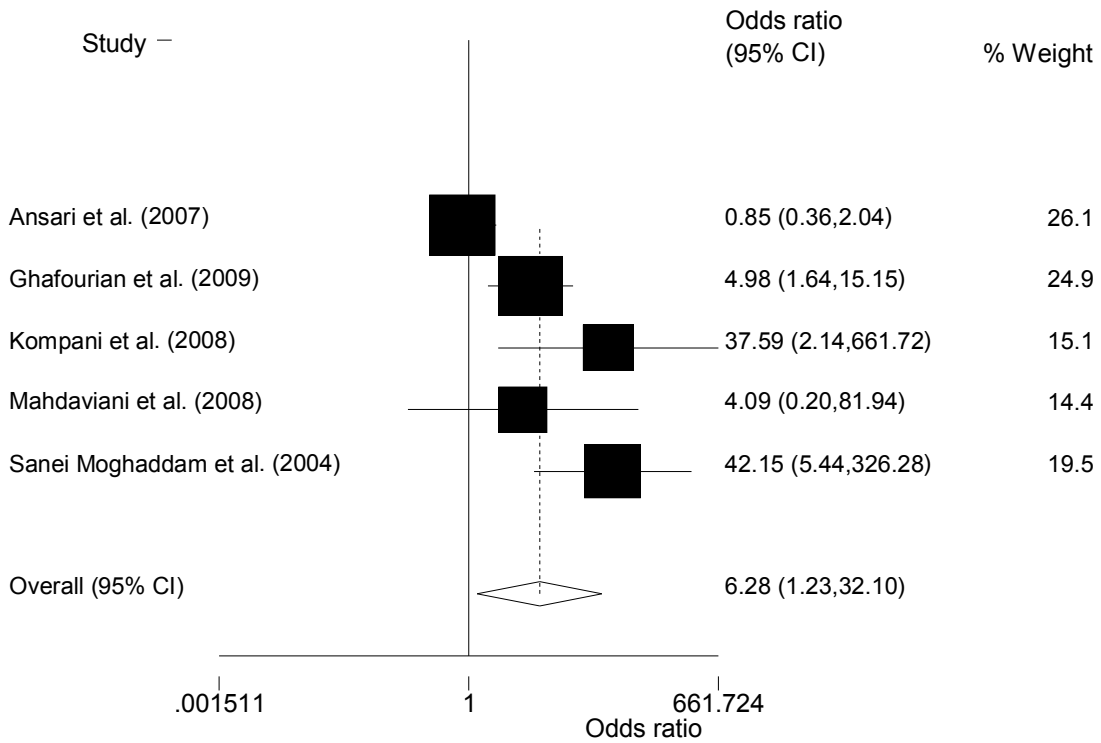

Fig. 5: Summary estimate of ORs with 95% confidence interval for positive HCV serostatus in Iranian thalassemia with high age versus low age patients (according to age groups defined within each study)

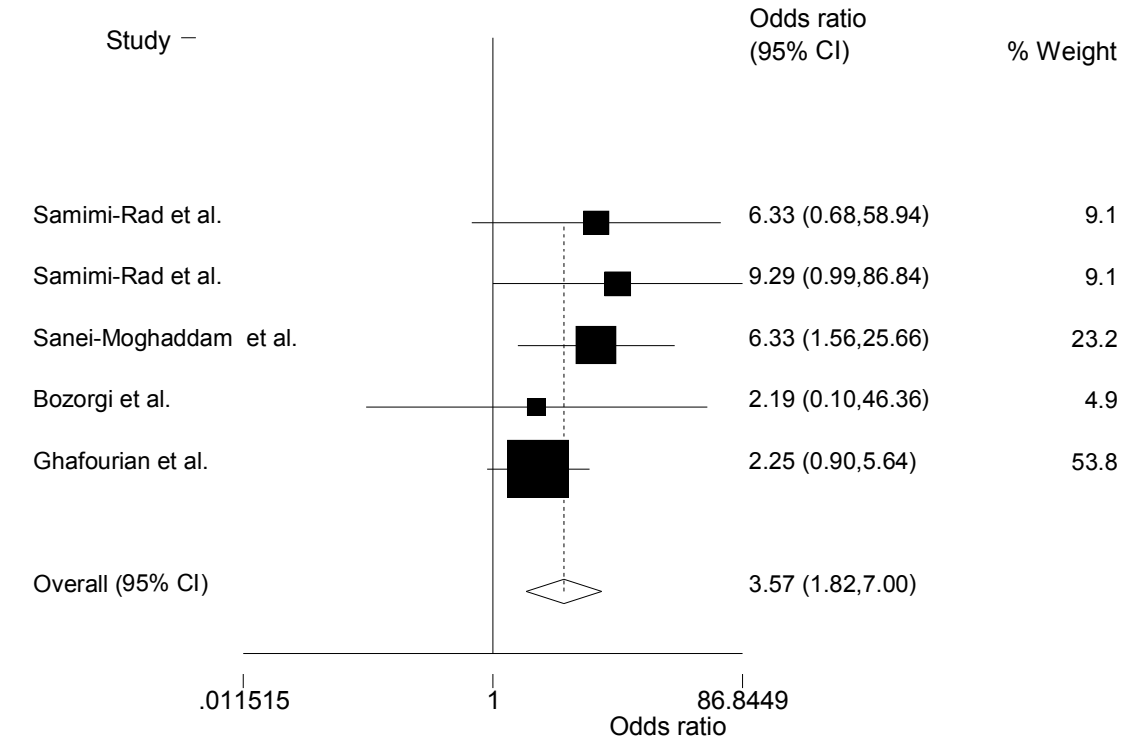

Fig. 6: Summary estimate of ORs with 95% confidence interval for positive HCV serostatus in Iranian thalassemia with high transfusion number versus low transfusion number patients (according to categories that were defined within each study)

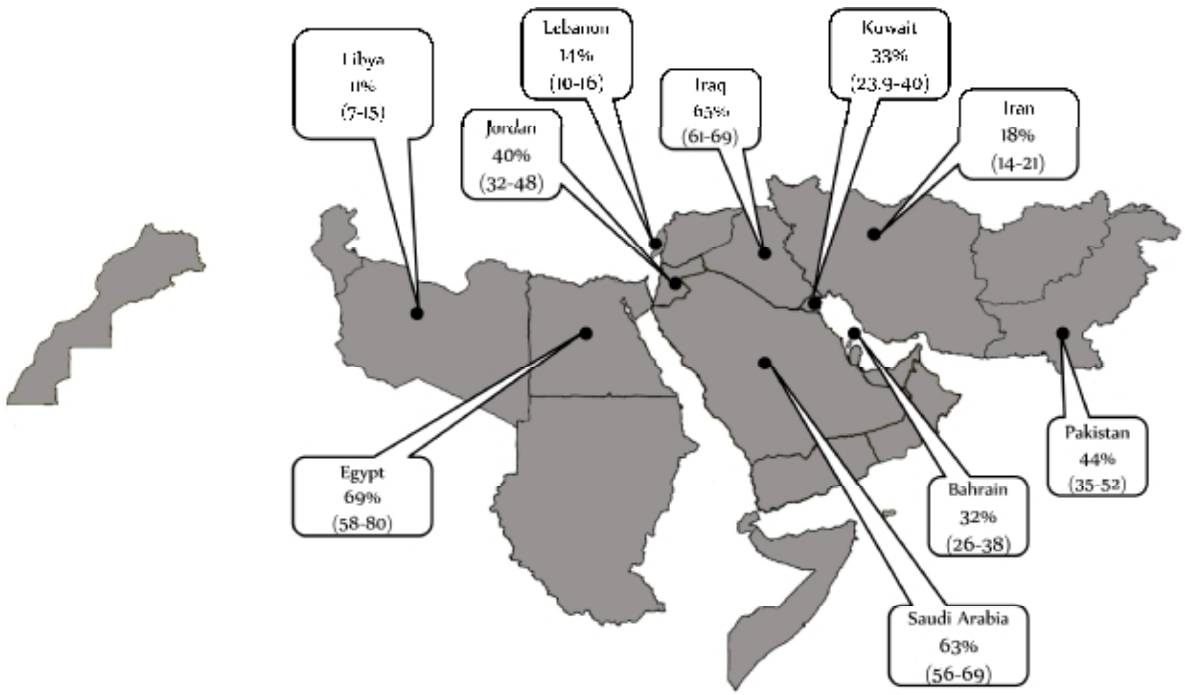

Fig. 7: Geographical distribution of pooled or individual epidemiology of HCV infection among thalassemia patients in EMRO

Table 3: HCV infection rates among polytransfused thalassemia patients from EMRO counties other than Iran

Country	Author Name	Publication year	Design	Sample size	ELISA	RIBA	age	Male (%)	Prevalence (%) 95% CI
Iraq	Al-Kubaisy et al.[44]	2006	C-S	559	3rd	Yes	2–10	NR	67 (63-71)
Pakistan	Akhtar et al.[45]	2004	C-S	256	3rd	No	NR	NR	34 (28-40)
	Mohammad et al.[46] *	2003	C-S	80	3rd	No			36 (25-47)
	Younus et al.[47]	2004	cohort	75	3rd	No	6.5	64	42 (31-53)
	Burki et al.[48] *	2005	C-S	180		No			42 (34-48)
	Shah et al.[49]	2005	C-S	250	NR	No	5-10 (43%)	72	57 (51-63)
	Moatter et al.[50]	1999	C-S	100	2nd	No	8	57	34 (25-43)
	Mukhtar et al.[51]	2005	C-S	250		No			57 (50-62)
	Hussain et al.[52] *	2008	C-S	180	NR	No	7	NR	42 (34-48)
Bahrain	al-Mahroos et al.[53]*	1995	C-C	242		No			32 (26-38)
Kuwait	Al-Fuzae et al.	1998		129					33 (23.9-40)
Jordan	Al-Sheyyab et al.[22]	2001	C-S	143	NR	No	9	61	40 (32-48)
Lebanon	Ramia et al.[54] *	2002	C-S	395		No			14 (10-16)
Saudi Arabia	Bahakim et al.[55] *	1991	C-C	78		No			33 (23-43)
	al-Fawaz et al.[56]	1996	C-C	28		No		51	57 (39-75)
	Al-Hawsawiet al.[57] *	2000		32					91 (80-100)
Egypt	el Gohary et al.[58]	1995	C-C	45	2nd	No	NR	NR	76 (64-88)
	el-Nanawy et al.[59] *	1995	C-C	18		No			44 (21-67)
Libya	Daw et al.[60] *	2002	C-C	250		No			11 (7-15)

The data from studies that are marked with asterisk are extracted from their abstract.

Discussion

The HCV infection is a widespread disease that affects a large number of thalassemia patients worldwide and is considered as a major public health problem in these high risk groups (OR=28.9, 95% CI 18.9-44). These patients act as a reservoir of this infection and are one of the main obstacles for HCV infection control in the community. The first transfusion before or after introduction of blood donors screening for anti-HCV antibody was the major determinant of HCV infection in the region. In Kuwait and Jordan, all of HCV infected thalassemia cases were transfused before blood donors screening (1992 in Kuwait and 1995 in Jordan).[21,22] In Iran, blood donors screening for HCV infection started in 1996. The pooled OR of HCV infection rate for patients transfused before that date was OR=7.6 (95% CI 4.7 -12.3). This

implies an increase in blood safety and more attention to health precautions in Iran[5,23,24] but data from other EMRO countries are inadequate and inconclusive.

Our systematic review showed that there was a strong gap in the current knowledge about blood safety in Eastern Mediterranean countries. The data were available from 50% of countries in this region and most of these data suffered the low sample size and outdatedness. Lack of knowledge about blood safety and the current serostatus of HCV infection as the most prevalent transfusion transmitted disease in thalassemia patients as a major consumer of blood is a major threat to public health of these countries. Most of the data from this region came from Iran. There were significant differences in provinces regarding HCV infection rates. The highest prevalence rate was seen in Semnan (32%, 95% CI 22-40) and the lowest in Zanjan (2%, 95% CI 0-6). The heterogeneous pattern of geographic distribution of HCV infection in thalassemia is different in different provinces and may be related to difference in the prevalence of HCV infection and risk factors in blood donors and general population.[25,26]

There is no data from many EMRO countries. Among the major EMRO countries, Iran has the least seroprevalence of HCV infection among thalassemia patients, indicating more advanced blood safety in this country compared with other countries with comparable population in this region.

Acknowledgement

The authors thank Research Center for Gastroenterology and Liver Disease, Baqiyatallah University of Medical Sciences for their support.

Conflict of interest: None declared.

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