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Seroprevalence versus Active HCV Infection in Hemophilia and Thalassemia Patients, Shiraz, Iran

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Abstract

Hepatitis C virus (HCV) is the one of the major infections transmitted through the bloodstream. Thalassemia and hemophilia patients because of regular blood transfusions are more prone to HCV infection. This study conducts to determine the prevalence of HCV, HCV viral load, genotype pattern and risk factors in thalassemia and hemophilia patients in Iran.

Among 4916 suspected HCV infection patients, referred to Prof. Alborzi Clinical Microbiology Research Center, Shiraz, Iran, from 2004 to 2019, the HCV seroprevalence rate and the HCV RNA load and genotypes was determined by the enzyme-linked immunosorbent assay and one-step Taq Man real-time PCR.

Among 4916 patients were assessed for the study, 440 were with thalassemia and 162 with hemophilia. The prevalence of HCV-Ab positivity among thalassemia and hemophilia patients was 58.9% and 87%, respectively. The most prevalent genotype was Gt-1, which was detected in 56.81% of the patients whose genotypes were assessed. The HCV viral load was generally higher among HCV seropositive patients compared to HCV seronegative patients.

Prevalence of hepatitis C among hemophilia and thalassemia patients was high. Since in these high-risk groups didn't find any independent risk factor for HCV, it can be concluded that multi-transfusion is the only predictor for hepatitis C.

Keywords: Hepatitis C Virus; Thalassemia; Hemophilia; Risk factors; Blood transfusion; Real-Time PCR

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Introduction

Thalassemia is rare hereditary hemoglobin disorders and it's endemic specially in the Mediterranean Area and South-East Asia [1]. world health organization (WHO) has reported one of the high-risk area for hepatitis C virus (HCV) is South Asia with prevalence rate of 2.1% [2]. Thalassemia is a rare inherited hemoglobin disorder and is endemic primarily in the Mediterranean region and Southeast Asia [1]. In addition, the World Health Organization (WHO) has reported that South Asia is one of the high-risk areas for hepatitis C virus (HCV) with a prevalence rate of 2.1% [2].Two clinical forms of thalassemia according to severity are distinguished: thalassemia major (TM), started during the first year of life and characterized by severe anemia, requiring regular transfusion therapy for survival, thalassemia intermedia (TI), distinguished by later onset and universally milder anemia, without regular transfusion therapy for survival [3]. The most common transfusion-transmitted infectious agents are HCV and HBV [4]. But, the most common cause of post-transfusion hepatitis (PTH) and end-stage liver disease in many countries is HCV, generally. Also, the cause of the second major epidemic of viral infection after human immunodeficiency virus (HIV) is HCV infection [5]. In patients with hereditary hemolytic anemia, especially thalassemia, regular blood transfusion has improved their overall survival, but carries a risk of acquisition of blood-borne virus infections, especially viral hepatitis [6, 7]. Many patients with β-thalassemia are infected with either HCV or HBV because of blood transfusion, especially patients who were received transfusion before the 1990. In reality, serological tests were available for detect infections in blood donors after 1990 [8].

Hemophilia is the result of coagulation factor deficiency. A decisive diagnosis of hemophilia A or B is based on an established family history and presentation of bleeding event in patients that has been confirmed by laboratory tests [9]. Most of children with hemophilia were infected with HCV before the HCV screening of blood products be available [10]. In Iran after implementation of compulsory blood donors screening in 1997, the rate of infection decreased significantly [11]. Hemophilia A is a rare, X-linked bleeding disorder that its prevalence almost is 1 of every 5000 to 10000 live-born males [12]. Hemophilia B is much less common than hemophilia A, with 1 of 25000 births prevalence [13].

While, post-transfusion transmission of HCV is a major health concern in patients with thalassemia; vaccination against hepatitis B efficiently restricts the transmission of hepatitis B virus (HBV) infection. Also, in patients with thalassemia HCV infection have a potentiating effect on hepatic fibrogenesis [14]. In addition, one of the progressive disease is chronic hepatitis C that due to liver failure or hepatocellular carcinoma causes increase of mortality rates among thalassemic patients [15]. Also, HCV is the major cause of chronic liver disease in hemophilic patients [16]. WHO suggested the screening of blood and blood products should be accomplished at least for HCV, HIV, HBV, syphilis and malaria parasites [17, 18]. About 10% to 50% of patients with HCV infection shown to clear infection naturally [11, 19, 20]. Apart from viral characteristics, cellular immune responses have an important role in viral clearance and disease resolution [19]. The prevalence of HCV infection among hemophilia patients that received unsterilized blood products is very high and reaching 90% in many countries [20,21]. According to evidences the prevalence of HCV infection in hemophilic patients is high and the risk of acquisition of HCV infection among hemophilic patients is higher than other hereditary bleeding disorders. HCV seropositive in hemophilic patients is relate with longer history of transfusion [22]. The prevalence of HCV infection among Iranian hemophilic patients has reported 15.6-76.7% [23]. Among hemophilia patients co-infection with HCV and HIV-1 is common [24]. Hemophilia and thalassemia patients are at high risk of transfusion-transmissible viruses (HCV, HBV and HIV). Because of HCV infection have the higher rate in these two groups, any co-infection with other viral hepatitis, particularly A can terminate to liver failure [25].

The aim of current study was to determine the prevalence of HCV among thalassemic and hemophilic patients. Although nowadays the prevalence of HCV in thalassemic and hemophilic patients in all societies has decreased, a new study to follow up the prevalence of this virus in these patients is very important.

Methods

In this cross-sectional study conducted between 2004 to 2019, 440 thalassemia and 162 hemophilia patients referred to the PACMRC, were assessed for HCV serostatus, viral load and genotypes. At first, 5 cc of clot blood sample was obtained by venipuncture at the PACMRC. Then, the samples were centrifuged, and its sera were stored in 1.5 mL vials at -70°C until examination. In the first step, we considered the antibodies against HCV infection for all patients included in the study using the GB anti-HCV V4.0 ELISA kit (Hsinchu science Park-Taiwan). In the next step, we extracted HCV RNAs from 200 µL serum of each specimen using Invitek kit (Berlin- Germany), based on the described guidelines. In the end, the HCV viral load and genotypes among all patients assessed. We used one-step Taq-Man real-time PCR HCV quantification and genotype kits (Genome Diagnostics Pvt. Ltd., Hague, Netherland) to perform HCV quantitative tests and genotyping. Based on manufacturer' instructions were used a 7500 real-Time PCR system (Applied Biosystems, USA). In all of patients the serostatus of HIV, HDV and HBV was determined, too. The study was confirmed by the Ethics and Research Committee of CMRC, Shiraz University of Medical Sciences, Shiraz, Iran.

Statistical Analysis

For the statistical analysis in this study, the chi-square test was used. All calculation of the data was performed using SPSS for Windows (Version 16.0, 2007, SPSS Inc., Chicago, IL, United States).

Results

The study included of 440 with thalassemic and 162 with hemophilic, whose samples were collected from 2004 to 2019. Their mean age was 25.88 years (range 2-62 years) and 34.35 years (range 4-74), respectively (**Table 1**). The HDV serology test was negative in all patients. The prevalence of HCV-Ab and HCV-RNA among all patients was 3865 /4916 (78.6%) and 2627/4916 (53.4%), respectively (Chart1). The results of viral serologic markers shown 186 (3.8%) and 5 (0.1%) of patients had HIV and HBV, respectively. But among thalassemia and hemophilia patients, the serology tests for HIV and HBV were negative.

Of 440 thalassemia patients, 262 (59%) tested seropositive for HCV, of whom only 111 (25.2%) had viremia, while for hemophiliacs, 141 of 162 (87%) patients had a positive serologic test, of which only 83 (51.2%) were positive.

A number of factors, which could be associated with HCV

Table 1. Demographic data of Iranian suspected HCV infection patients.

Variables	General Patients	Thalassemia Patients	Hemophilia Patients
Age Average (y)	40.34	25.88	34.35
Age range	Jan-98	Feb-62	Apr-74
Sex (male/female)	3838/1077	213/227	133/28
Total	4916	440	162
Variables	General Patients	Thalassemia Patients	Hemophilia Patients
Age Average (y)	40.34	25.88	34.35
Age range	Jan-98	Feb-62	Apr-74
Sex (male/female)	3838/1078	213/228	133/29

infection, were compared between HCV-seropositive and seronegative patients with thalassemia and hemophilia using the univariate analysis. The results of these are summarized in (**Tables 2** and **Table 3**). According to these tables, none of factors were not associated with HCV infection in thalassemic and hemophilic patients ($p > 0.05$). Also, some factors such as addiction, injection, tattoo, prisoner, phlebotomy and working in vet didn't exist among thalassemia patients but other patients with these factors infected with HCV. About hemophilia patients needling, transplant cirrhosis, phlebotomy and pregnancy were factors that didn't exist in these patients.

From 4916 suspected HCV infection patients 262 (5.32%) had undergone soft organ transplant procedures, of which 173 (66%) were liver transplant, 86 (33%) were kidney transplant, 2 (1%) were bone marrow transplant, and 1 (0.5%) was a heart transplant. Moreover, 4654 (94.7%) had not received any transplant. The HCV response to treatment rate among HCV-infected patients who had organ transplantation was lower than HCV-infected patients without transplantation (1.5 vs. 47.2%).

Finally, the HCV viral load, genotypes and the relationship between HCV antibody and viral load were determined. All the patients were referred between 1 to 9 times for HCV tests and 2627 (5343%) of them showed HCV viremia and genotyping was done in 389 (7.91%) patients.

The lowest and the highest viral loads were 200 and 12,952,483,200 copy/ml, respectively among general population while it was 500 and 500,000 among these patients. The most prevalent genotype was Gt-1, which was determined in 221 (56.81%) patients, followed by Gt-3 in 161 (41.38%), Gt-2 in 3 (0.77%), Gt-4 in 2 (0.51%) and Gt-13 in 2 (0.51%) patients. Among thalassemic (59.37%) and hemophilic (69.76%) patients Gt-1 was the most prevalent genotype, followed by Gt-3 in 12 (37.5%) and 13 (30.23%) thalassemic and hemophilic patients, respectively.

In the end, the results of our study displayed viral load among HCV-seronegative patients is lower than HCV-seropositive patients.

As shown in (**Figure 1**), a significantly lower percentage of thalassemia patients have active HCV viremic infection compared to hemophiliacs and general HCV-infected patients.

Also, we obtain significant difference between HCV-Ab positive and HCV-RNA positive among thalassemia, hemophilia and all patients (p value <0.005).

Table 2. Comparison of factors between HCV-seropositive and HCV-seronegative Iranian thalassemia patients (N=440).

Factors	HCV positive	HCV negative	P value
Sex	-	-	0.174
	128 (29.1%)	99 (22.5%)	-
Female	134 (30.5%)	79 (18%)	-
	0	2 (0.5%)	0.163
Male	6 (1.4%)	1 (0.2%)	0.25
HIV	-	-	-
Hemophilia	-	-	-
Needling	1 (0.2%)	0	1
Surgery	1 (0.2%)	0	1
Transplant	-	-	-
	2 (0.5%)	0	0.517
Liver	-	-	-
Cirrhosis	1 (0.2%)	0	1
Pregnancy	1 (0.2%)	0	1

Table 3. Comparison of risk factors between HCV-seropositive and HCV-seronegative Iranian hemophilic patients (N=161).

Factors	HCV positive	HCV negative	*P* value
Sex	-	-	0.122
	22 (13.7%)	6 (3.7%)	
Female	119 (73.9%)	14 (8.7%)	
Male	-	-	
Dialysis	0	1 (0.6%)	0.123
Addiction	7 (4.3%)	0	0.598
Injection	4 (2.5%)	0	1
Prisoner	1 (0.6%)	0	1
Tattoo	5 (3.1%)	0	1
Vet	2 (1.6%)	1 (0.8%)	0.285
Thalassemia	6 (3.7%)	1 (0.6%)	1
Surgery	15 (9.4%)	1 (0.6%)	0.695
Tattoo	6 (3.1%)	0	0.695

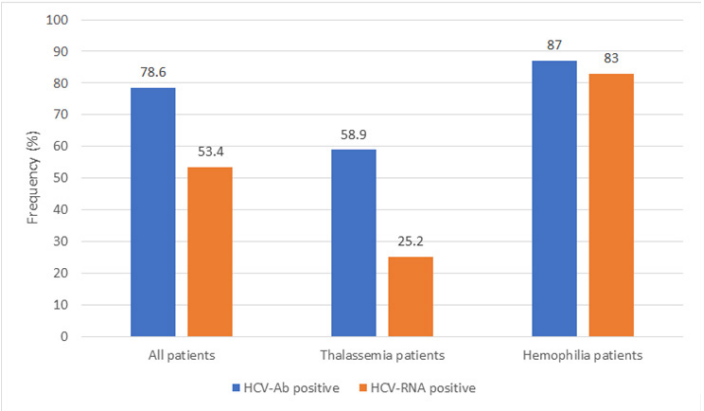

Figure 1. Prevalence of HCV-Ab positive and HCV-RNA positive among thalassemia, hemophilia and all patients. In hemophilia patients the rate of HCV infection was higher than thalassemia patients. Moreover, in all patients which might have other risk factors of HCV infection, the rate of infection was lower than hemophilia patients but it was higher than thalassemia patients.

Discussion

Thalassemia is a hereditary anemia with need of lifelong blood transfusion. This causes patients with thalassemia become vulnerable to viral disease [26,27]. In the other hand, the risk of HCV transmission has not been eliminated while the currently developed prevention protocols [28,29]. So, because of most patients with HCV are asymptomatic, the periodic screening of patients is necessary. Furthermore, information about the immunological status of patients is important [30,31]. Generally, the prevalence of HCV infection in the Iranian population is low but among thalassemia patients is almost high. Therefor these patients are at high risk for developing HCV infection[32,33]. In addition, based on a recent systematic review and meta-analysis, in Iran, the most prevalent HCV genotype is Gt-1 specially subtype 1a (42%), followed by Gt-3 specially subtype 3a (35%)

[34]. Worldwide, genotype 1 is the predominant genotype (49.1%), followed by genotypes 3 (17.9%), 4 (16.8%) and 2 (11%) [35]. Keshvari et el, in the previous study reported the most prevalent HCV genotypes among Iranian hemophilic patients was Gt-1a followed by Gt-3a and 1b [36]. This results were similar to Western Europe and different from Middle East region [33]. Also, among thalassemia patients positive for HCV, these genotypes are prevalent (47). Our study indicates the same results, too. One study in Shiraz conducted by Jamalidoust et al, indicated Gt-3 was the most prevalent genotype among high risk group patients such as hemodialysis [37]. So, we concluded among different high-risk groups, common genotype can be different. Significantly, the risk of post-transfusion infection has reduced; for example, in the united states it has reached 1 in 100,000 [38,39]. For identifying subjects who are at risk, advanced screening techniques were effective [40]. In Iran, we observed a decline in the prevalence of HCV in the past years [41]. Iran detected as a country with a low frequency of HCV infection, too [42]. Iran is one of the countries that use of screening techniques has been very effective in decline the transmission of various diseases through blood transfusion [43]. Prior to these developments, the prevalence of HCV (95%) and HBV (68%) infection among hemophilic patients in Poland were high [44]. Whereas in the general population the rates were significantly lower (0.6%) [44,45]. In Shiraz, Southern Iran, 15.7% of thalassemic children with a history of multiple transfusion were positive for anti-HCV (58). Other single-center-studies reported prevalence of HCV infection had wide range (16-64%) on Iranian thalassemic patients [46-47]. Alavian et al, revealed prevalence of positive anti-HCV among Iranian thalassemic patients was 24.2%. The countries with a higher prevalence of HCV infection in general population had a higher prevalence among thalassemia patients, too [48]. For example, in India the HCV prevalence was low among both of blood donors (1.78%) and thalassemia patients (25.5%). Seroprevalence rate of HCV among thalassemia patients was 39.2% in Pakistan [49]. In our study the HCV seropositive among thalassemia pateints was relatively high (58.9%). The prevalence of HCV infection in thalassemic patients in Kuwait was 33% [50]. Also, among thalassemic patients in Bahrain and Jordan the rate of HCV was 40%. Study on hemophilic patients in Tehran from 2003 to 2005 showed the prevalence of positive anti-HCV antibody was 72.3% and accented on the screening of hemophilic patients for HCV infection. HCV infection prevalence among thalassemia and hemophilia patients was high 59.5% and 87.7% in this study. Furthermore, in current study we didn't find any independent risk factor for HCV among thalassemia and hemophilia patients. Some studies in Iran and other countries reported similar results in hemophilia patients [51]. But other study in Brazil showed some factors such as age were significantly associate to HCV infection among hemophilic patients. Previous study conducted by Ghafourian et al, showed mean age in thalassemic patients with positive HCV antibody was significantly higher than negative subjects. In our study the prevalence of HCV infection among all patients was higher than thalassemic and hemophilic patients. So, we considered data and understand some patients without thalassemia and hemophilia, were affected other risk factors such as addiction, HIV, needling and transplant. For example, 1543 (39.3%) and 1536 (39.1%) of positive HCV patients were addicted without thalassemia and hemophilia respectively. Also, 169 (4.3%) of positive patients were coinfected with HIV and didn't have hemophilia and thalassemia. Jamalidoust et al, reported patients with HCV infection are prone for infected with HIV and other types of hepatitis. In the other hand, HCV infection is one of the common reasons for liver transplantation in end-stage cirrhosis. So it's important to considered the effect of HCV among the recipients.

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Conflict of Interest

The authors declare no conflict(s) of interest.

Ethical Approval statement

The project has been approved by Shiraz University of Medical Sciences

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