Hepat Mon. 2018 October; 18(10):e69395. doi: 10.5812/hepatmon.69395.

Published online 2018 October 13. **Research Article**

Update on Transmission Modes of Hepatitis C Virus Among Volunteer Iranian Blood Donors: Analysis of a Matched Case-Control Study by Penalized Conditional Logistic Regression

Fahimeh Ranjbar Kermani [1], Kamran Mousavi Hosseini [1,*], Sedigheh Amini Kafi-abad [1], Mahtab Maghsudlu [1], Zohreh Sharifi [1], Mohammad Ali Mansournia [2] and Seyed Moayed Alavian [3,4]

[1] Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran
[2] Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[3] Baqiyatallah Research Center for Gastroenterology and Liver Diseases (BRCGL), Baqiyatallah University of Medical Sciences, Tehran, Iran
[4] Middle East Liver Diseases (MELD) Center, Tehran, Iran

[*] *Corresponding author*: Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran. Email: mkmousavi@yahoo.com

Received 2018 April 14; **Revised** 2018 September 02; **Accepted** 2018 September 16.

Abstract

Background: Reducing the risk of transfusion transmitted infections (TTI) is one of the main concerns of blood transfusion systems. Evaluation of HCV risk factors in HCV infected blood donors is critical for donor selection and ensuring blood safety. The aim of this study was to evaluate known and putative risk factors of HCV infection in Iranian blood donors.

Methods: This matched case-control study was conducted on serologically confirmed HCV positive blood donors (cases) and serologically negative HCV blood donors came back to Iranian Blood Transfusion centers over the country from November 2015 to May 2017. Cases and controls were matched by donation status and interviewed for demographic, medical, and risk histories. Penalized conditional logistic regression model with backward selection method was used in data analysis. STATA software version 13 was used for statistical analysis.

Results: A total of 271 cases and 794 controls were interviewed. Age (AOR (5 year), 1.27; 1.13 - 1.42), intravenous drug abuse (AOR, 24.89; 10.2 - 60.82), religious self-flagellation (AOR, 7.02; 2.02 - 24.4), non-injecting drug abuse (AOR, 6.13; 2.49 - 15.13), history of blood transfusion (AOR, 5.22; 1.52 - 17.92), imprisonment (AOR, 4.81; 2.43 - 9.53), sharing personal razor (AOR, 4.55; 1.45 - 14.28), tattooing (AOR, 4.46; 2.37 - 8.38), extramarital sexual activity (AOR, 2.88; 1.40 - 5.87), cupping in outpatient place (AOR, 2.44; 1.08 - 5.52), tooth extraction (AOR, 2.35; 1.46 - 3.78), surgery (AOR, 1.98; 1.22 - 3.21), and intramuscular injection (AOR, 1.68; 1.06 - 2.68) found to be current independent risk factors for HCV infection demonstrated in 98.52% of cases.

Conclusions: This is the first study to perform penalized conditional logistic regression model in data analyzing to control some statistical bias in the evaluation of HCV risk factors among Iranian blood donors. According to the results, intravenous drug abuse is a primary HCV risk factor. In addition, the study emphasizes on the role of other high-risk behaviors such as religious self-flagellation and high-risk procedures such as cupping in outpatient place in HCV transmission. Increasing donor education regarding HCV risk factors and more accurate donor selection needs to improve blood safety and protect recipients from potential HCV infection risk.

Keywords: Risk Factor, Blood Donors, Hepatitis C, Case-Control, Iran

1. Background

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease associated with a high global prevalence of morbidity and mortality (1, 2). Approximately 115 million individuals have HCV antibodies worldwide (3, 4). The prevalence of HCV infection varies in different regions, ranging from less than 1.5% in low-prevalence regions to approximately 10% in high-prevalence regions (4). The seroprevalence of HCV ranges from 0.08% to 1.6% in different provinces of Iran, with an overall prevalence of 0.6% (5). In addition, the rate of HCV seropositivity in blood donors ranges from 0.003% to 1.8% in different countries (6).

HCV seropositivity, estimated at 0.05% in Iranian blood donors, has decreased over the past decade (7). HCV is transmitted through both parenteral and non-parenteral routes. In developed and developing countries, drug injection and blood transfusion, without HCV screening during blood donation, are the most common routes of HCV infection, respectively. In addition, nosocomial transmission of

HCV appears to be the most common risk factor in some developing countries with HCV screening for blood donors (3, 8-10).

One of the main concerns of blood transfusion systems is to reduce the risk of transfusion-transmitted infections. Although the risk of HCV transmission has markedly reduced with improvements in HCV screening methods for blood donation, there is a residual risk of transfusion-transmitted HCV, even in developed countries where molecular methods are implemented for HCV screening during blood donations (11). Generally, the most important approach for improving blood safety is to select donors who do not have the risk factors for transfusion-transmissible infections and to reduce unnecessary deferral of safe donors (12).

Annually, over 2,100,000 whole blood units are collected in Iran (13). According to a study from Iran performed in 2013, over one-quarter of prospective blood donors were deferred due to donor or recipient safety (14). The high number of discarded donations and deferred donors indicates the role of donor selection criteria in blood safety. Evaluation of HCV risk factors in HCV-infected blood donors is critical for donor selection, as a key step in the selection process is to apply a proper questionnaire, based on the current risk factors (12).

Elimination of HCV infection by 2030, using new direct-acting antiviral (DDA) agents, is the current strategy of the global health sector, which was approved in the 69th World Health Assembly (15). Considering the recent availability of DAAs with high efficacy in Iran, case findings and therapy are suggested as the best strategies for HCV prevention (16). Besides the importance of identifying HCV risk factors in the donor selection, these factors play an essential role in HCV case findings in the general population.

In addition, implementation of some preventive measures, such as raising awareness in the general population and healthcare system about the routes of HCV transmission, requires knowledge about HCV risk factors. Due to the inaccessibility of vaccines for HCV prevention, researchers have focused on the regular analysis of HCV risk factors in different populations to clarify the current routes of HCV transmission around the world (17-26). Overall, the significance of HCV risk factors varies in different populations and regions. Intravenous drug use (IDU) or non-intravenous drug use (non-IDU) before HCV screening for blood donations, extramarital sexual activity, medical interventions, tattooing, living with an IDU abuser, imprisonment, and use of shared personal razors are some common risk factors for HCV infection in Iran (18, 27-29).

Considering the time-dependent changes in the epidemiology of HCV infection, which can represent changes in HCV risk factors (30), and presence of previous risk factors in the community, it is important to determine the current risk factors. Accordingly, the aim of this study was to evaluate the known and putative risk factors for HCV infection in Iranian blood donors.

2. Methods

This matched case-control study was conducted on volunteered blood donors who were referred to the Iranian Blood Transfusion Organization (IBTO) from November 2015 to May 2017. According to the standard operating procedures (SOPs) of IBTO, prospective donors are considered eligible for blood donation if they met all the criteria for blood donation. The subjects are examined and interviewed by a trained physician to complete the questionnaire. Ineligible prospective donors are deferred temporarily or permanently, based on the examiner's assessment. In addition, there are options of self-deferral and confidential unit exclusion before donation for the participants. Donations were tested serologically for HBV, HCV, HIV, and syphilis in 7 provinces of Iran for human T-lymphotropic virus (HTLV) 1,2. All reactive donations on the enzyme-linked immunosorbent assay (ELISA, Enzygnost Anti-HCV 4.0 Kit; Siemens, Germany) were discarded, and the donors were permanently deferred. Repeatedly reactive donations were subjected to serological confirmatory recombinant immunoblot assay (RIBA) and HCV BLOT 3.0 (MP Diagnostics). Donors whose donations were positive on the confirmatory test were requested to return to the blood transfusion center for notification and consultation by trained physicians.

2.1. Case and Control Groups

Confirmed HCV-positive blood donors were included in the case group, while HCV-negative blood donors were recruited in the control group. The case and control groups showed no positive results on other screening tests, including HBV, HIV, syphilis, or HTLV 1,2.

2.2. Selection of Case and Control Groups

Serologically confirmed HCV-positive blood donors, who were referred to the blood transfusion centers to repeat the HCV screening test or receive consultation, were selected as the case group; the subjects were willing to participate in the study. On the other hand, serologically confirmed HCV-negative blood donors, who agreed to participate in this study, were randomly selected from the same blood centers; we attempted to recruit these participants at the same time as the case group. Due to confounding effect of first time donation (18), the groups were matched in terms of the donation status. For this purpose, three

types of donors were classified with respect to the donation status according to the IBTO definition: first-time, repeat, and regular donors (7). To evaluate the association between demographic characteristics and HCV infection, no further matching measures were taken in the control and case groups.

2.3. Risk Factor Questionnaire and Interview

A post donation questionnaire was developed in a previous study through consulting IBTO experts (18), focusing on demographic characteristics and possible HCV transmission according to international and national studies on HCV risk factors. This questionnaire has been applied in previous research to evaluate the risk factors for HCV among Iranian blood donors (18) and was only revised in the present study. All case and control subjects were interviewed by trained physicians to complete identical questionnaires.

The questionnaire included the following items: (1) demographic characteristics, such as age, gender, marital status, and education; (2) high-risk behaviors, such as IDU, inhalation drug abuse, religious self-flagellation/scarification, and extramarital sexual activity; (3) medical interventions, such as blood transfusion, hospitalization, surgery, endoscopy, dental treatments (e.g., tooth extraction, gum surgery, root canal treatment, and dental implants), suturing, acupuncture, and needle stick injury treatments; and (4) high-risk practices, such as tattooing, cupping, and body piercing. The questionnaires, which were completed all over the country, were sent to the research team in Tehran.

2.4. Ethical Considerations

This study was approved by the Ethics Committee of High Institute for Research and Education in Transfusion Medicine, Tehran, Iran (code, IR.TMI.REC.1394.1800).

2.5. Statistical Analysis

Demographic characteristics, as well as known and putative risk factors, were considered as the independent variables, while HCV status was regarded as the dependent variable. To determine the role of blood transfusion and cupping in HCV transmission, they were classified in subgroups. Blood transfusion was classified as blood transfusion before and after HCV screening for blood donation and cupping was categorized as cupping in hygienic and outpatient (traditional) clinics in Iran. In the analyses, independent variables with more than 2 categories, such as educational level, were integrated as dummy variables. The univariate association between 60 independent variables and HCV status was assessed via conditional logistic regression; the results were summarized as crude odds ratio (OR) at 95% confidence interval (CI). For variables with sparse data distribution, penalization was applied via data augmentation, using the log-F (1,1) prior. To adjust for confounding factors, analyzing too many independent variables and avoid sparse data bias, penalized logistic regression model with a backward selection algorithm was applied at an alpha level of 0.05. The results were summarized as adjusted ORs (AORs) at 95% CI (31-33). All independent variables with P-values below 0.2 on the univariate analysis were considered to have significant effects and were included in the multivariable analysis. All analyses were performed using STATA version 13 (STATA Corp., College Station, Texas, USA).

Table 1. Baseline Characteristics of 271 Cases (HCV- Positive Blood Donors) and 794 Controls (HCV-Negative Blood Donors) Blood Donors Participating in This Study, Iran 2015 - 2017[a]

Characteristic	Controls	Cases
Age, y	32.99 ± 9.97	37.87 ± 8.61
Gender		
Male	712 (89.67)	262 (96.68)
Female	82 (10.33)	9 (3.32)
Marital status		
Single	248 (31.39)	58 (21.72)
Married	532 (67.34)	202 (75.66)
Divorced	7 (0.89)	5 (1.87)
Widow	3 (0.38)	2 (0.75)
Educational level		
Under diploma	209 (26.49)	165 (62.26)
Diploma	280 (35.49)	67 (25.28)
Associate	91 (11.53)	11 (4.15)
Bachelor and higher	209 (26.49)	22 (8.30)

[a] Values are expressed as mean ± SD (standard deviation) or No. (%). The sum of numbers is not exactly the total number of subjects, due to missing values and the total of percentages is not exactly 100, due to rounding the values.

3. Results

During the study, a total of 271 and 794 subjects were recruited in the case and control groups, respectively and interviewed. First-time donors (94.5%) constituted the majority of subjects, followed by repeat donors (3.7%) and regular donors (1.9%). Baseline characteristics of 271 cases and 794 controls is shown in Table 1.

On the univariate analysis, a significant increase was reported in the risk of anti-HCV positivity in 37 out of 60 independent variables, which were classified into 4 cate-

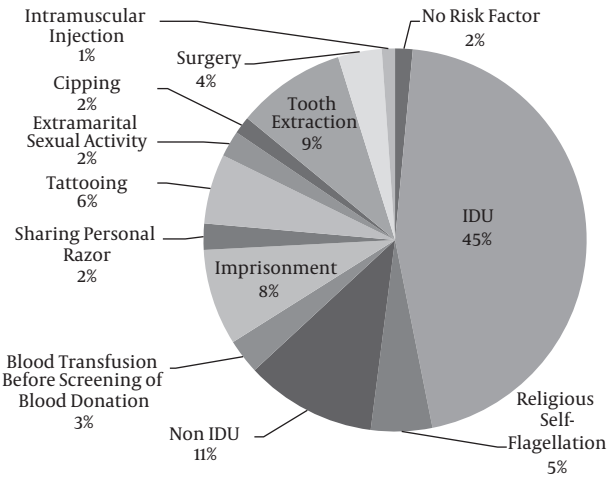

Figure 1. The hierarchy of the proportion of cases based on the strongest risk factor illustrated in Table 3, Iran 2015 - 2017

gories as described in materials and methods section (Table 2).

After applying penalized logistic regression with backward selection, a total of 13 independent variables remained as significant risk factors for HCV infection (Table 3).

Some cases had more than one risk factor, as presented in Table 3. Among 271 HCV-positive cases, 74.17% had a history of high-risk behaviors, 16.97% had a history of medical interventions, and 7.38% had a history of high-risk procedures. The order of risk factors, relative to the proportion of cases with the strongest risk factors, is shown in Figure 1.

4. Discussion

Evaluation and update of HCV risk factors in HCV-infected blood donors is critical for donor selection and ensuring blood safety. In this matched case-control study, we evaluated the known and putative risk factors for HCV infection among Iranian HCV-positive blood donors. The results revealed current risk factors for HCV transmission in blood donors, including age, IDU, religious self-flagellation/scarification, inhaled drug abuse, history of blood transfusion before screening for blood donation, history of imprisonment, shared personal razors, history of tattooing, extramarital sexual activity, cupping in an outpatient setting, tooth extraction, history of surgery, and history of intramuscular injection.

The present findings showed that IDU is by far the strongest risk factor for HCV infection, which is in accordance with several studies (18, 20-22, 27, 34-36). Moreover, shared injection equipment, history of tattooing, and history of imprisonment are some independent risk factors for HCV among ID users (37).

The results also revealed that non- DU is one of the HCV risk factors in blood donors, as reported in several studies (27, 28, 38).

We observed a significant relationship between HCV infection and history of blood transfusion before screening for blood donation, which is similar to the results of different studies from diverse geographical regions (18-21, 27, 28, 34-36, 39). However, we did not observe any association between blood transfusion after blood donation screening and HCV infection. The results of this study highlight the importance of implementing safety measures all over the country by Iranian blood transfusion centers.

Our findings confirm that extramarital sexual activity is a risk factor for HCV in Iranian blood donors, although the association is weaker than previously reported (AOR, 2.96 vs. 42.2 in 2002 and 8.52 in 2016) (18, 27). In Western countries, the role of heterosexual activity in HCV transmission is insignificant (40) and substituted by male homosexual activities (10). Moreover, history of imprisonment showed a strong association with HCV infection, which is in accordance with some previous studies (18, 29, 36). Although in the multivariable analysis, the confounding effects of other independent variables such as IDU and tattooing, as common practices among prisoners, history of imprisonment, was remained in the final model. It is estimated that 38% - 88.9% of IDU prisoners are infected with HCV in different parts of Iran (41, 42).

In the present study, tattooing was found to be associated with HCV infection. Some studies have revealed that tattooing with unsafe materials and equipment is one of the routes of HCV transmission. This finding is quite similar to the results of a recent meta-analysis, showing that tattooing is a strong risk factor for HCV infection in blood donors (OR, 4.46; CI, 2.37 - 8.38 vs. OR, 4.09; CI, 2.8 - 5.98) (43). In addition, cupping in outpatient settings was found to be a route of HCV transmission. Although cupping in the healthcare setting was associated with HCV infection in the univariate analysis, it was eliminated as a risk factor in the final model. Overall, cupping therapy, as an alternative method of treatment, is used in some countries and has been reported as a route of HCV transmission (44, 45).

There are controversies regarding the association between dental treatments and HCV. Our results confirmed that HCV can transmit through dental treatments, which is consistent with other studies (22, 29, 46). In a meta-analysis of 357 studies and literature review, dental treatment was suggested as a route of HCV transmission (47, 48). Similar to the results of a previous research, tooth extraction was found to have an association with acquiring HCV infec-

Table 2. Univariate Comparison of Known and Putative Risk Factors Associated with HCV Infection, Iran, 2015 - 2017

Independent Variables	Cases, N = 271 (%)	Controls, N = 794 (%)	OR (95% CI)
Demographic characteristics			
Male gender	712 (96.68)	262 (89.67)	3.38 (1.66 - 6.91)
Getting married	202 (75.66)	532 (67.34)	1.52 (1.1 - 2.11)
Age (5 year)[a]	-	-	1.30 (1.21 - 1.40)
High risk behaviors			
Injecting drug abuse	123 (45.39)	7 (0.88)	86.65 (40.62 - 184.87)
Sex with injecting drug abusing partner	9 (3.32)	0 (0.00)	53.47 (3.09 - 924.63)
Inhalation drug abuse	90 (33.21)	8 (1.01)	45.70 (22.21 - 94.03)
Living with injecting drug abuser	32 (11.81)	2 (0.25)	42.07 (11.52 -153.58)
History of sexually transmitted disease	7 (2.58)	0 (0.00)	41.1 (2.33 - 725.57)
History of imprisonment	129 (47.60)	24 (3.02)	28.38 (17.78 - 45.28)
Knife-injury	56 (20.66)	8 (1.01)	22.94 (10.45 - 50.36)
Self-injury	47 (17.41)	7 (0.88)	21.97 (10.03 - 48.15)
Religious self- flagellation	28 (10.33)	6 (0.76)	13.86 (5.84 - 32.92)
Living with a patient with viral hepatitis	19 (7.01)	4 (0.50)	13.11 (4.65 - 36.97)
Sharing of razor	32 (11.81)	8 (1.01)	12.3 (5.7 - 26.54)
Extramarital sexual activity	95 (35.06)	33 (4.16)	11.24 (7.11 - 17.77)
Living with icteric person	19 (7.01)	7 (0.88)	7.85 (3.34 - 18.48
Sex with icteric/ hepatic partner	6 (2.21)	2 (0.25)	7.06 (1.6 - 30.87)
Alcohol consumption	107 (39.48)	73 (9.19)	6.37 (4.53 - 8.97)
Sharing of tooth brush	9 (3.32)	4 (0.50)	5.97 (1.92 - 18.6)
Contact sport	64 (19.93)	120 (15.11)	1.48 (1.00 - 2.17)
Medical interventions'			
Needle stick	19 (7.01)	2 (0.25)	23.64 (6.28 - 88.98)
Blood transfusion before screening of donations	12 (4.43)	5 (0.63)	6.89 (2.42 - 19.59)
Acupuncture	4 (1.48)	2 (0.25)	6 (1.1 - 32.76)
Tooth extraction	206 (76.01)	219 (40.18)	5.95 (4.15 - 8.53)
Blood transfusion after screening of donations	9 (3.32)	6 (0.76)	4.27 (1.5 - 12.03)
Wound at war	11 (4.06)	9 (1.13)	3.84 (1.54 - 9.61)
Suturing	54 (19.93)	57 (7.18)	3.55 (2.30 - 5.47)
Dental implants	16 (5.90)	15 (1.89)	3.36 (1.60 - 7.03)
History of hospitalization	59 (21.77)	69 (8.69)	3.33 (2.20 - 5.04)
History of surgery	132 (48.71)	191 (24.06)	3.11 (2.31 - 4.19)
History of intramuscular injection	141 (52.03)	258 (32.49)	2.65 (1.93 - 3.63)
History of intravenous injection	91 (33.58)	157 (19.77)	2.36 (1.677 - 3.31)
History of endoscopy of upper part of digestive system	23 (8.49)	30 (3.78)	2.28 (1.31 - 3.94)
Tooth surgery	14 (5.17)	20 (2.52)	2.10 (1.05 - 4.21)
High risk procedures			
Tattooing	102 (37.64)	35 (4.41)	12.84 (8.46 - 19.47)
Cupping in outpatient place	41 (15.13)	24 (3.02)	6.67 (3.72 - 11.96)
Cupping in hygienic center	33 (12.18)	50 (6.30)	2.35 (1.40 - 3.94)

Abbreviations: OR, odds ratio; CI, confident interval.
[a] Age are calculated according to 5 years increasing in age.

Table 3. Backward Penalized Regression Model of Risk Factors Associated with HCV Infection, Iran 2015 - 2017

Risk Factors	AOR (95% CI)	P Value
Injecting drug abuse	24.89 (10.2 - 60.82)	0.000
Religious self-flagellation	7.02 (2.02 - 24.4)	0.002
Inhalation drug abuse	6.13 (2.49 - 15.13)	0.000
Blood transfusion before screening of donations	5.22 (1.52 - 17.92)	0.009
History of imprisonment	4.81 (2.43 - 9.53)	0.000
Sharing of personal razor	4.55 (1.45 - 14.28)	0.009
History of tattooing	4.46 (2.37 - 8.38)	0.000
Extramarital sexual activity	2.88 (1.40 - 5.87)	0.004
Cupping in outpatient place	2.44 (1.08 - 5.52)	0.03
Tooth extraction	2.35 (1.46 - 3.78)	0.000
History of surgery	1.98 (1.22 - 3.21)	0.005
History of intramuscular injection	1.68 (1.06 - 2.68)	0.03
Age (5 year)[a]	1.27 (1.13 - 1.42)	0.000

Abbreviations: AOR, odds ratio; CI, confident interval.
[a] Age are calculated according to 5 years increasing in age.

tion in the present study (49). Overall, it seems that tooth extraction by unprofessional staff, who work in substandard hygienic conditions in outpatient dental settings, are responsible for HCV transmission via tooth extraction in Iran.

A remarkable finding of this study was the association of religious self-flagellation/scarification with HCV infection. Considering the unhygienic nature of this ritual act, it is highly liable to be a route of transmission for some infections. Based on a study conducted in Pakistan, self-scarification was significant in HBV transmission (50). Moreover, according to unpublished data by Iran Hepatitis Network, religious self-scarification is a risk factor for HCV in Iran, Iraq, and Lebanon. Additionally, a large-scale study on blood donors from the United States revealed that religious scarification was a risk factor for HCV (34).

In the present study, gender, marital status, educational level, and occupation were not associated with the higher risk of HCV infection. Age was found to be an independent risk factor for HCV infection. The results showed an increase of 20% in the OR of HCV infection for every 5-year increase in the donor's age. The results of a previous study on HCV patients during 2010-2015 showed that all age groups were associated with HCV infection (51). On the other hand, in a previous study on Iranian blood donors, the association between age and HCV positivity could not be evaluated due to age matching (18), while in another study, no association was reported in blood donors, without age matching or grouping (27). Nonetheless, another study on American blood donors showed that older age was associated with HCV (20).

Although, some current HCV risk factors are similar to those reported in the previous case- control study on Iranian blood donors (18), such as IDU, inhaled drug abuse, history of blood transfusion before screening for blood donation, history of imprisonment, shared personal razors, and extramarital sexual activity; except for history of blood transfusion before screening for blood donation, the association was higher in the presented study than those of this study odds ratios: 24.89, 6.13, 5.22, 4.81, 4.55, 2.88 compare to 6.42 3.37, 8.54, 2, 2.4, 1.97, respectively. As in the presented study, based on donation status, we designed a matched case-control study and reported that 94.5% of subjects were first time donors, the odds ratios of risk factors of first time donors were just compared. Considering that penalized conditional logistic for analyzing a matched case- control study data was performed in the presented study, the discrepancies may be explained by differences in study design and statistical methods.

In the present study, evaluation of behavioral, medical, and cultural factors, as well as other high-risk factors, was integrated in the post donation questionnaire. The routes of HCV infection were identified in 98.5% of HCV-infected blood donors in the present study versus 75.5% and 88.8% of Iranian blood donors in previous studies (27, 28).

To ensure generalizability of the study, we selected cases and controls from the same blood transfusion center all over the countries and they were interviewed in the same time and matched by donation status. The present study had some limitations. The interview was conducted among blood donors who accepted to participate in this study and might not be a representative of all blood donors and were eligible for the study. Therefore, the identified risk factors might have been influenced due to possible differences in the risk profiles of participants and non-participants. In addition, similar to all case-control studies, we encountered a recall bias. Furthermore, since the interviewers were not blind to the results of HCV test in the case group, underestimation of the prevalence of risk factors is possible in the controls. Moreover, the prevalence of some independent variables was very low or very high; therefore, a penalized conditional logistic regression model was performed in data analysis to control some statistical bias in the evaluation of HCV risk factors among Iranian blood donors.

In conclusion, our findings indicated IDU as the most important and primary risk factor for HCV infection. The role of religious self-flagellation as the second most important route of HCV transmission was highlighted in Iranian blood donors. Surgery and intramuscular injection were found to be poorly associated with HCV infection and

should be elucidated cautiously. Our findings highlighted some risk factors in Iranian blood donors, which were integrated in the donor selection process, but were not disclosed by prospective donors because of unawareness of HCV risk factors. In addition, some prospective donors, who were aware of HCV risk factors, knew that if they disclosed their risk factors, they would be no longer eligible for donation; even uninfected donors were unwilling to disclose some behaviors. It is possible that blood donors pay less attention to the educational measures introduced by IBTO. Although donor selection seems to be effective in Iran (52), increasing the knowledge of prospective blood donors regarding the routes of HCV transmission and conducting more accurate interviews by physicians can lead to more successful donor selection and high blood safety. Finally, the present results can be applied in the surveillance of HCV infection in Iran to prevent this disease in the general population.

Acknowledgments

This article is part of the result of a PhD by research thesis in Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine. We wish to thank the Institute for the financial and moral support.

Footnote

Funding/Support: This study was supported by High Institute for Research and Education in Transfusion Medicine, Research Center of Blood Transfusion, Tehran, Iran.

References

1. Lavanchy D. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect*. 2011;**17**(2):107–15. doi: 10.1111/j.1469-0691.2010.03432.x. [PubMed: 21091831].
2. Cooke GS, Lemoine M, Thursz M, Gore C, Swan T, Kamarulzaman A, et al. Viral hepatitis and the Global Burden of Disease: A need to regroup. *J Viral Hepat*. 2013;**20**(9):600–1. doi: 10.1111/jvh.12123. [PubMed: 23910643].
3. Lanini S, Easterbrook PJ, Zumla A, Ippolito G. Hepatitis C: /Global epidemiology and strategies for control. *Clin Microbiol Infect*. 2016;**22**(10):833–8. doi: 10.1016/j.cmi.2016.07.035. [PubMed: 27521803].
4. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol*. 2014;**61**(1 Suppl):S45–57. doi: 10.1016/j.jhep.2014.07.027. [PubMed: 25086286].
5. Mirminachi B, Mohammadi Z, Merat S, Neishabouri A, Sharifi AH, Alavian SH, et al. Update on the prevalence of hepatitis C virus infection among Iranian general population: A systematic review and meta-analysis. *Hepat Mon*. 2017;**17**(2). doi: 10.5812/hepatmon.42291.
6. World Health Organization. *Blood safety and availability. WHO fact sheet*. WHO; 2016. Available from: http://www.who.int/news-room/fact-sheets/detail/blood-safety-and-availability.
7. Amini Kafi-Abad S. Blood safety overview in Iran. *Arch Iran Med*. 2015;**18**(10).
8. World Health Organization. *Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection*. Geneva, Switzerland: WHO; 2016.
9. Liakina V, Hamid S, Tanaka J, Olafsson S, Sharara AI, Alavian SM, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries - volume 3. *J Viral Hepat*. 2015;**22 Suppl 4**:4–20. doi: 10.1111/jvh.12475. [PubMed: 26513445].
10. European Association for Study of Liver. EASL clinical practice guidelines: Management of hepatitis C virus infection. *J Hepatol*. 2014;**60**(2):392–420. doi: 10.1016/j.jhep.2013.11.003. [PubMed: 24331294].
11. Leparc GF. Safety of the blood supply. *Cancer Control*. 2015;**22**(1):7–15. doi: 10.1177/107327481502200103. [PubMed: 25504274].
12. World Health Organization. *Blood donor selection: Guidelines on assessing donor suitability for blood donation*. Geneva: WHO; 2012.
13. Maghsudlu M. Keys to move to self-sufficiency in safe blood components based on voluntary blood donation. *ISBT Sci Serie*. 2017;**12**(1):202–6. doi: 10.1111/voxs.12344.
14. Birjandi F, Gharehbaghian A, Delavari A, Rezaie N, Maghsudlu M. Blood donor deferral pattern in Iran. *Arch Iran Med*. 2013;**16**(11):657–60. [PubMed: 24206408].
15. Polaris Observatory H C V Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. *Lancet Gastroenterol Hepatol*. 2017;**2**(3):161–76. doi: 10.1016/S2468-1253(16)30181-9. [PubMed: 28404132].
16. Alavian SM, Hajarizadeh B, Bagheri Lankarani K, Sharafi H, Ebrahimi Daryani N, Merat S, et al. Recommendations for the clinical management of hepatitis C in Iran: A consensus-based national guideline. *Hepat Mon*. 2016;**16**(8). e40959. doi: 10.5812/hepatmon.guideline. [PubMed: 27799966]. [PubMed Central: PMC5075356].
17. Alavian SM, Hatami S. [The evaluation of acute viral hepatitis patients referred to tehran hepatitis center with regard to etiology and risk factors (2000-2001)]. *Govaresh J*. 2016;**6**(33-34):125–30. Persian.
18. Rezaei N, Amini-Kafiabad S, Maghsudlu M, Abolghasemi H. Risk factor analysis of hepatitis C virus seropositivity in Iranian blood donors: A case-control study. *Transfusion*. 2016;**56**(7):1891–8. doi: 10.1111/trf.13660. [PubMed: 27273657].
19. Huang Y, Guo N, Yu Q, Lv Y, Ma H, Yun Z, et al. Risk factors for hepatitis B and C infection among blood donors in five Chinese blood centers. *Transfusion*. 2015;**55**(2):388–94. doi: 10.1111/trf.12850. [PubMed: 25382751].
20. Custer B, Kessler D, Vahidnia F, Leparc G, Krysztof DE, Shaz B, et al. Risk factors for retrovirus and hepatitis virus infections in accepted blood donors. *Transfusion*. 2015;**55**(5):1098–107. doi: 10.1111/trf.12951. [PubMed: 25470984]. [PubMed Central: PMC4428964].
21. Mitrovic N, Delic D, Markovic-Denic L, Jovicic M, Popovic N, Bojovic K, et al. Seroprevalence and risk factors for hepatitis C virus infection among blood donors in Serbia: A multicentre study. *Dig Liver Dis*. 2015;**47**(7):572–6. doi: 10.1016/j.dld.2015.03.019. [PubMed: 25882212].
22. Czerwinski M, Grabarczyk P, Stepien M, Kubicka-Russel D, Tkaczuk K, Brojer E, et al. What weighs more-low compliance with self-deferral or minor medical procedures? Explaining the high rate of hepatitis C virus window-period donations in Poland. *Transfusion*. 2017;**57**(8):1998–2006. doi: 10.1111/trf.14163. [PubMed: 28555775]. [PubMed Central: PMC5703057].
23. Khan ZA, Shafiq M, Shahab F. Frequency and risk factors of hepatitis b and c in Afghan patients presenting to Tertiary Care Hospital in Peshawar. *Pakistan Arm Forc Med J*. 2015;(5):686.
24. Hussein NR, Saleem ZSM. An outbreak of hepatitis C virus at a renal dialysis unit: A lesson from a war zone. *Int J Infect*. 2016;**In Press**(In Press). doi: 10.17795/iji-39763.
25. Sharma S, Sharma AK, Sujatha R, Bansal A. Risk factors of hepatitis C infection in patients of chronic liver disease in a rural area of Uttar Pradesh. *India J Sci Res*. 2016;**7**(1):193.

26. Arshad A, Ashfaq UA. Epidemiology of hepatitis C infection in pakistan: Current estimate and major risk factors. *Crit Rev Eukaryot Gene Expr*. 2017;**27**(1):63–77. doi: 10.1615/CritRevEukaryotGeneExpr.2017018953. [PubMed: 28436333].
27. Alavian SM, Gholami B, Masarrat S. Hepatitis C risk factors in Iranian volunteer blood donors: A case-control study. *J Gastroenterol Hepatol*. 2002;**17**(10):1092–7. doi: 10.1046/j.1440-1746.2002.02843.x. [PubMed: 12201870].
28. Hajiani E, Hashemi J, Masjedizadeh R, Shayesteh AA, Idani E, Rajabi T. Seroepidemiology of hepatitis C and its risk factors in Khuzestan Province, south-west of Iran: A case-control study. *World J Gastroenterol*. 2006;**12**(30):4884–7. doi: 10.3748/wjg.12.4884. [PubMed: 16937474]. [PubMed Central: PMC4087626].
29. Vossoughinia H, Taghi Shakeri M, Mokhtari Amirmajdi E, Abedini S. [Risk factors for hepatitis B and C in 400 blood donor volunteers in Mashhad During 2003-2007: A case-control study]. *Horizon Med Sci*. 2010;**15**(4):68–75. Persian.
30. Alavian SM. Hepatitis C virus infection: Epidemiology, risk factors and prevention strategies in public health in IR IRAN. *Gastroenterol Hepatol bed bench*. 2009;**3**(1).
31. Greenland S, Mansournia MA. Penalization, bias reduction, and default priors in logistic and related categorical and survival regressions. *Stat Med*. 2015;**34**(23):3133–43. doi: 10.1002/sim.6537. [PubMed: 26011599].
32. Greenland S, Mansournia MA, Altman DG. Sparse data bias: A problem hiding in plain sight. *BMJ*. 2016;**352**. i1981. doi: 10.1136/bmj.i1981. [PubMed: 27121591].
33. Mansournia MA, Geroldinger A, Greenland S, Heinze G. Separation in logistic regression: Causes, consequences, and control. *Am J Epidemiol*. 2018;**187**(4):864–70. doi: 10.1093/aje/kwx299. [PubMed: 29020135].
34. Murphy EL, Bryzman SM, Glynn SA, Ameti DI, Thomson RA, Williams AE, et al. Risk factors for hepatitis C virus infection in United States blood donors. NHLBI retrovirus epidemiology donor study (REDS). *Hepatology*. 2000;**31**(3):756–62. doi: 10.1002/hep.510310329. [PubMed: 10706569].
35. O'Brien SF, Fan W, Xi G, Yi QL, Goldman M, Fearon MA, et al. Declining hepatitis C rates in first-time blood donors: Insight from surveillance and case-control risk factor studies. *Transfusion*. 2008;**48**(5):902–9. doi: 10.1111/j.1537-2995.2007.01618.x. [PubMed: 18208409].
36. Brandao AB, Fuchs SC. Risk factors for hepatitis C virus infection among blood donors in southern Brazil: A case-control study. *BMC Gastroenterol*. 2002;**2**:18. doi: 10.1186/1471-230X-2-18. [PubMed: 12169200]. [PubMed Central: PMC122085].
37. Woltmann J, Burke P, Brady R, Blackard JT. Demographics of hepatitis C in Southwest Ohio (2010 to 2015). *Hepat Mon*. 2016;**16**(8). e37904. doi: 10.5812/hepatmon.37904. [PubMed: 27799964]. [PubMed Central: PMC5075223].
38. Orton SL, Stramer SL, Dodd RY, Alter MJ. Risk factors for HCV infection among blood donors confirmed to be positive for the presence of HCV RNA and not reactive for the presence of anti-HCV. *Transfus*. 2004;**44**(2):275–81. doi: 10.1111/j.1537-2995.2004.00623.x. [PubMed: 14962320].
39. Al-Waleedi AA, Khader YS. Prevalence of hepatitis B and C infections and associated factors among blood donors in Aden City, Yemen. *East Mediterr Health J*. 2012;**18**(6):624–9. [PubMed: 22888620].
40. Terrault NA, Dodge JL, Murphy EL, Tavis JE, Kiss A, Levin TR, et al. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: The HCV partners study. *Hepatology*. 2013;**57**(3):881–9. doi: 10.1002/hep.26164. [PubMed: 23175457]. [PubMed Central: PMC4384338].
41. Zobeiri M, Adibi P, Alavian SM. Intravenous drug use and hepatitis C virus in iran. *Hepat Mon*. 2012;**12**(1):9–10. doi: 10.5812/kowsar.1735143X.797. [PubMed: 22451838]. [PubMed Central: PMC3298870].
42. Taherkhani R, Farshadpour F. Epidemiology of hepatitis C virus in Iran. *World J Gastroenterol*. 2015;**21**(38):10790–810. doi: 10.3748/wjg.v21.i38.10790. [PubMed: 26478671]. [PubMed Central: PMC4600581].
43. Khodadost M, Maajani K, Arabsalmani M, Mahdavi N, Tabrizi R, Alavian SM, et al. Is tattooing a risk factor for hepatitis c transmission?: An updated systematic review and meta-analysis. *hepat Mon*. 2017;**17**(9). doi: 10.5812/hepatmon.14308.
44. Madani TA. Hepatitis C virus infections reported in Saudi Arabia over 11 years of surveillance. *Ann Saudi Med*. 2007;**27**(3):191–4. doi: 10.5144/0256-4947.2007.191. [PubMed: 17568177]. [PubMed Central: PMC6077082].
45. Chandra M, Khaja MN, Farees N, Poduri CD, Hussain MM, Aejaz Habeeb M, et al. Prevalence, risk factors and genotype distribution of HCV and HBV infection in the tribal population: A community based study in south India. *Trop Gastroenterol*. 2003;**24**(4):193–5. [PubMed: 15164530].
46. Tanwandee T, Piratvisuth T, Phornphutkul K, Mairiang P, Permpikul P, Poovorawan Y. Risk factors of hepatitis C virus infection in blood donors in Thailand: A multicenter case-control study. *J Med Assoc Thai*. 2006;**89 Suppl 5**:S79–83. [PubMed: 17722300].
47. Dahiya P, Kamal R, Sharma V, Kaur S. "Hepatitis" - Prevention and management in dental practice. *J Educ Health Promot*. 2015;**4**:33. doi: 10.4103/2277-9531.157188. [PubMed: 26097847]. [PubMed Central: PMC4456879].
48. Mahboobi N, Porter SR, Karayiannis P, Alavian SM. Dental treatment as a risk factor for hepatitis B and C viral infection. A review of the recent literature. *J Gastrointestin Liver Dis*. 2013;**22**(1):79–86. [PubMed: 23539395].
49. Al-Kubaisy MW, Bobryshev YV, Shamsidah Ni N, Al-Naggar RA, Al-Kubaisy W. Is dental extraction a risk factor for contracting HCV infection: Abs, RNA and genotype detection. *Oral Biol Dentistr*. 2014;**2**(1):7. doi: 10.7243/2053-5775-2-7.
50. Abdulla EM, Abdulla FE. Seropositive HBSAG frequency in Karachi and interior Sindh, Pakistan. *Pak J Med Sci*. 2007;**23**(2):157–60.
51. Sharhani A, Mehrabi Y, Noroozi A, Nasirian M, Higgs P, Hajebi A, et al. Hepatitis C Virus seroprevalence and associated risk factors among male drug injectors in Kermanshah, Iran. *Hepat Mon*. 2017;**17**(10). doi: 10.5812/hepatmon.58739.
52. Razjou F, Maghsudlu M, Nasizadeh S, Zadsar M. The impact of donor selection on blood safety in Iran. *Transfus Apher Sci*. 2012;**47**(1):13–6. doi: 10.1016/j.transci.2012.03.001. [PubMed: 22521567].