Comprehensive investigation of the prevalence and risk factors of viral hepatitis B and C in PERSIAN Guilan Cohort Study

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Abstract

Background Hepatitis B (HBV) and C (HCV) viruses are two serious infectious diseases with high global health impact. The aim of this study was to evaluate the prevalence of HBV and HCV in the Prospective Epidemiological Research Studies of the Iranian Adults (PERSIAN) Guilan Cohort Study through immunological and molecular methods.

Methods The blood samples were obtained from 10520 enrolled participant. Complete biochemical and hematological assessments plus urine analysis were done. The presence of HBsAg, anti-HBs, anti-HBc and anti-HCV antibodies for all participants and HBeAg and anti-HBe antibody for HBV positive patients were evaluated. HBV genomic DNA and HCV genomic RNA were extracted from positive serum samples. Real time PCR assay was done to quantify HBV and HCV genomes. HCV genotyping was also performed.

Results Most of our participants were female (53.5%), rural (56.1%), married (97.2%) with primary education (72.1%) without smoking (75.2%) or alcohol consumption (85.3%). The HBV and HCV prevalence was 0.24% (95% CI, 0.16% to 0.35%) and 0.11% (95% CI, 0.06% to 0.19%), respectively. Rural participants were significantly more HBV positive than urban peoples ($P=0.045$) while male individuals were significantly more HCV positive than female participants ($P=0.013$).

Conclusion Our detected HBV and HCV prevalence were lower than other cities/provinces of Iran, which may be due to the lifestyle or other unknown reasons.

Background

The hepatitis B virus (HBV) is a viral agent whose target tissue is liver and can cause both acute and chronic illnesses [1]. According to the 2016 World Health Organization (WHO) statistics, 240 million people who are positive for at least 6 months of HBsAg are reported as HBV positive individuals [2]. Meaningly, more than 686,000 people die each year due to the effects of the virus, including cirrhosis and cancer [3]. Finally, the highest rates of hepatitis B are found in Africa and East Asia [4-7].

The hepatitis C virus (HCV) is the main cause of chronic liver disease, which can lead to chronic hepatocellular carcinoma with high economic burden [8-11]. It has silent epidemiology and at the same time is a major blood-borne infection worldwide [12]. According to the latest global health statistics, 130-150 million people are infected with HCV [13] and 700,000 people die each year [14]. HCV has seven genotypes and 70 subtypes. HCV RNA assays are the most sensitive test for HCV infection and are a gold standard for proving hepatitis C infection [15]. Between 1990 and 2013, global viral hepatitis deaths increased from 0.89 million (95% uncertainty interval [UI] 0.86–0.94) to 1.45 million (1.38–1.54) [16]. Base on one modeling study in 2016, the global prevalence of HBsAg was 3.9% (95% uncertainty interval [UI] 3.4-4.6) [17].

Therefore, Iran is classified as low to intermediate prevalence areas [18]. The last updated meta-analysis about HBV prevalence in Iran, show that among general population approximately 2.2% in 2016 [19].

Although certain population sub-groups such as hemophiliacs and hemodialysis are more susceptible to HBV and HCV [20-25], but evaluation of the prevalence of these two viruses in general population also is very important. Considering the importance of hepatitis B and C in this study, the prevalence of these viruses in people referring to the cohort of Guilan province will be discussed.

Methods

Participants

This study is nested in the Guilan center of Prospective Epidemiological Research Studies of the Iranian Adults (PERSIAN) cohort study [26, 27], which named PERSIAN Guilan Cohort Study (PGCS). The PGCS was started at September 2014 in Some'e Sara (GPS coordinator Latitude: 37.308003 & Longitude: 49.315022), Guilan, Northern of Iran. All residents between 35 to 70 years were enrolled. These 10520 peoples will be followed at least for 10 years to understand new diseases and identify the underlying genetic susceptibility factors for chronic diseases. Moreover, participants were followed up yearly by telephone or medias and they were encouraged to participate in the study. Peoples who were unable to attend the clinic for examination or refusal by a person to participate in the study were excluded [28].

Sampling and biochemical assessments

The aseptic blood samples were collected from the cubical vein into vacutainers. Total number of WBC, RBC, platelet, lymphocyte, monocyte, and granulocytes were counted. The serum sample was harvested and stored at -20 °C until use for complete biochemical assessment. The Hb concentration and level of Hct, MCV, MCH, MCHC, RDWCV, RDWSD, plateletcrit, MPV, PDW were also evaluated. Urine sample was collected and used immediately for measuring of specific gravity (SG), pH, and creatinine level.

Virological assessments

The presence of HBsAg, anti-HBs, anti-HBc and anti-HCV antibodies were determined by Electrochemiluminescence (Cobas e 411, Roche, Germany). For positive patients, these four tests plus presence of HBeAg and anti-HBe antibody were measured again. HBV genomic DNA was extracted from positive serum samples by viral DNA extraction kit (QIAGEN, Germany). HCV genomic RNA was extracted from positive serum samples by viral RNA extraction kit (Roche, Germany). To quantify HBV and HCV genomes, qPCR assay was carried out using TaqMan-based commercial available kit (QIAGEN, Germany) based on the manufacturer's instructions. HCV genotyping was done using HCV Genotype Plus Real-TM kit (Sacase Biotechnologies, Italy).

Ethical consideration

This study was confirmed by the Ethics Committee of Guilan University of Medical Sciences (Ethics code: IR.GUMS.REC. 1396.254).

Statistical analysis

Qualitative data were expressed as frequency and percentage and their association with HBV and HCV statuses were analyzed using Chi square test. Quantitative data were presented as mean $\pm$ SD and between HCV/HBV positive and negative groups differences were analyzed using two independent sample t test. All statistical analysis were performed using SPSS version 23. The P value lesser than 0.05 was considered as significant difference.

Results

Demographic characteristics of our patients and statuses of HBV and HCV infection are presented in Table 1. Most of our participants were female (53.5%), rural (56.1%), married (97.2%) with primary education (< 12 years) (72.1%) without smoking (75.2%) or alcohol consumption (85.3%). In addition, most of them had history of surgery (63.3%) and hospitalization (80.6%) and had no transfusion (89.5%) or genital aphthous (98.8%). The HBV prevalence was 0.24% (95% CI, 0.16% to 0.36%) and the HCV prevalence was 0.11% (95% CI, 0.06 % to 0.19 %). The geographic distribution of HBV positive and HCV positive patients based on gender are presented in Figure 1. Rural participants were significantly more HBV positive than urban peoples (P=0.045) while male individuals were significantly more HCV positive than female participants (P=0.013). No other significant associations were detected between other evaluated demographic variables with HBV and HCV prevalence.

The complete blood and urine analysis of our participants are presented in Table 2. HBV positive patients had significant lower platelet count (P=0.043), RDWCV (P=0.023), cholesterol (P=0.033), LDL (P=0.043) and LDL: HDL ratio (P=0.002) compared to HBV negative participants. HCV positive patients had significant higher MCH (P=0.036), MCHC (P=0.047), AST (P=0.032), ALT (P=0.030) and HDL (P=0.039) and significant lower LDL (P=0.028) and LDL: HDL ratio (P=0.001) compared to HCV negative individuals.

The viral load of 25 HBV positive and 12 HCV positive patients are presented in Table 3. Most HBV positive patients (52%) had lesser than 300 copies of HBV DNA per ml. While, most HCV positive patients

(58.4%) had 10^5 - 10^6 copies of HCV RNA per ml. Most detected HCV genotype was 2a (Figure 2). First-degree relatives of all HCV positive patients were also checked for HCV infection by qPCR. Just child of one patients had HCV infection with genotype similar to her mother as 1a.

Discussion

In the present study, the prevalence of HBV and HCV in the Guilan site of PERSIAN cohort were reported. We found the prevalence of 0.2 and 0.1 for HBV and HCV, respectively. Moreover, rural participants were significantly more HBV positive while male individuals were significantly more HCV positive. Finally, HBV positive patients had significant lower platelet count, RDWCV, cholesterol, LDL and LDL: HDL ratio and HCV positive patients had significant higher MCH, MCHC, AST, ALT and HDL and significant lower LDL and LDL:HDL ratio compared to related negative individuals.

The prevalence of HBV and HCV is very difference worldwide, which is related to geographical region and demographic factors. In 2015, it has been reported that HBV sero-prevalence was 8.83% (0.48 - 22.38) in African region, 0.81% (0.20 - 13.55) in Americas region, 3.01% (0.67 - 14.77) in Eastern Mediterranean region, 2.06% (0.01 - 10.32) in European region, 1.90% (0.82 - 6.42) in South East Asian region, 5.26% (0.37 - 22.70) in Western Pacific region [4]. In addition, there are several diversity in HBV prevalence between different states/provinces of each country. Since 2006 when the national vaccination program for peoples who born after 1993 were started and continued, an obvious decrease in the HBV prevalence was seen [29]. Therefore, Iran is classified as low to intermediate prevalence areas [18]. Although our detected rate of HBV infection is too lower than reported pooled HBV prevalence in Iran among general population (2.2%) in 2016 [19], it is approximately similar to our previous report about volunteer blood donors as 0.45 - 0.48% [30, 31] and to reported rates from Karaj as 0.4% [32], Kermanshah as 0.7% [33] and Kurdistan as 0.8% [34]. Also, our reported HBV infection rate is lower than those reported from Birjand as 1.6% [35], Tehran, Golestan, and Hormozgan as 2.6% [36], and Nahavand as 2.3% [37]. In addition, some population sub-groups are more likely susceptible to have HBV. For instances in our province, 71.3% of hemophiliacs [22], and 0.38 - 3.8 % of hemodialysis patients [20, 21, 23] were HBV positive. We found that men are more HBV positive than women (16 vs. 9 cases) which is similar to previous reports from Iran about higher prevalence of HBV infection in men [19, 38].

The pooled HCV prevalence of 0.3%, 6.2%, and 32.1% were reported for general, intermediate- and high-risk Iranian populations, respectively [39]. Again, diversities between different cities/provinces and subgroups are seen. It has been reported that all healthy adults of Isfahan [40] and Mashhad [41], blood donors of Tehran [42], Ardabil [43], and Ahvaz [44], infertile male of Tehran [45], and male blood donor of Tabriz [46] were HCV negative. Our detected HCV prevalence (0.1%) is lower than pooled HCV prevalence of Iranian general population as 0.3% [39] and is differed from previous report from Rasht as 0.03% and Guilan as 0.32% [47]. Also, our detected HCV prevalence is lower than other reported prevalence from Northern provinces of Iran. For instance, HCV prevalence was 0.48% in Babol [48], and 0.18 - 1% in Golestan [49-51]. However, Zamani et al. reported similar HCV prevalence as 0.08% in general population of Mazandaran province [52]. Higher male HCV positivity, as seen in our study, was also reported

previously from Kerman province [53], Zahedan [54], and Kavar [55]. However, in opposite to our study, Ghadir et al. reported that female were more HCV positive compared to male in general population of Golestan [49]. Finding of one woman who her daughter also was HCV positive and both had same HCV genotype highlighted the clear role of interfamilial HCV transmission and confirmed the significant role of close relatives which reported previously [56].

Although, we detected no significant associations between demographic variables and prevalence of HBV and HCV, but it seems that different demographic features of population in different regions are the most important reasons for these differences in HBV and HCV prevalence. Base on Baig's study the male to female ratio of HBV increased during the reproductive years. There may be an influence of estrogen in the protection and defense of hepatic cells against the development of chronic liver disease [57]. In Zeng et.al study married people had the highest prevalence of HBsAg [58], on the other hand in Ataei et.al study in Isfahan province no statistical difference observed in terms of marital status but males (OR= 3.79) had higher prevalence of HBV than women [59].

About biochemical analysis, we found some significant differences. Among them, decrease of LDL and subsequently LDL: HDL ratio in both HBV and HCV positive patients compared to negative ones are interesting. These are in line with those reported recently as significant hypolipidemia in HBV [60] and HCV [61] patients. Lower platelet count in HBV positive, as we found in this study, also reported previously [62]. It can be said that, both HBV and HCV influenced the liver tissue and the changes in biochemical and hematological parameters can be related to these changes in the hepatic functions.

Conclusions

In summary, we found lower HBV and HCV prevalence compared to other regions of Iran. Also, compared to previous reports from our province, Guilan, the HBV and HCV prevalence also decreased. This may be due to the preventive strategy or increase of the medical knowledge of peoples, which must be evaluated in the further studies.

Abbreviations

HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, HBcAg: Hepatitis Core Antigen, HBsAg: Hepatitis B Surface Antigen

Declarations

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Author contributions

Study conception and design: F.J, A.SH and F.M

Acquisition of data: M, S, AA.S, A.S and S.Y

Statistical analysis: M.N, S.S, M.S and S.H

Interpretation of results: F.J, F.M, EP and S.H

Drafting of manuscript: F.J, S.Y, A.S and S.H

All authors approved the final version of the article, including the authorship list

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Ethics approval and consent to participate

Ethical approval of the study was obtained from Guilan University of Medical Sciences. (Grant number: 1397.163). Written consent was taken after informing the purpose and importance of the study to each participant. To ensure confidentiality of participant's information, codes were used where by the name of the participant and any identifier of participants was not written on the questionnaire.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Mean and SD of quantitative variables plus frequency and percentage of qualitative variables in total participants and based on HBV and HCV statuses.

Variables	Total	HBV		P value	HCV		P value
		Positive	Negative		Positive	Negative	
Age (year)	51.52±8.90	54.48±9.04	51.51±8.90	0.095	54.08±10.79	51.51±8.89	0.317
BMI (kg/m ²)	28.15±5.82	26.32±4.00	28.16±5.82	0.114	26.49±3.66	28.16±5.83	0.323
Gender				0.078			0.013
Male	4887 (46.5)	16 (0.3)	4871 (99.7)		9 (0.2)	4878 (99.8)	
Female	5633 (53.5)	9 (0.2)	5624 (99.8)		3 (0.1)	5630 (99.9)	
Habitat				0.045			0.108
Urban	4619 (43.9)	6 (0.1)	4613 (99.9)		7 (0.1)	4612 99.9)	
Rural	5901 (56.1)	19 (0.3)	5882 (99.7)		5 (0.1)	5896 (99.9)	
Marital status				0.490			0.647
Married	10224 (97.2)	25 (0.2)	10199 (99.8)		12 (0.1)	10212 (99.9)	
Single	296 (2.8)	0 (0)	296 (100)		0 (0)	296 (100)	
Education				0.301			0.673
Primary (< 12 years)	7590 (72.1)	21 (0.3)	7569 (99.7)		10 (0.1)	7580 (99.9)	
Diploma (12 years)	2284 (21.7)	4 (0.2)	2280 (99.8)		2 (0.1)	2282 (99.9)	
Academic (> 12 years)	646 (6.1)	0 (0)	646 (100)		0 (0)	646 (100)	
Smoking				0.861			0.943
Yes	2577 (24.5)	5 (0.2)	2572 (99.8)		3 (0.1)	2574 (99.9)	
No	7908 (75.2)	20 (3)	7888 (99.7)		9 (0.1)	7899 (99.9)	
Not-sure	7 (0.1)	0 (0)	7 (100)		0 (0)	7 (100)	
Alcohol consumption				0.497			0.900
Yes	1515 (14.4)	4 (0.3)	1511 (99.7)		2 (0.1)	1513 (99.9)	
No	8977 (85.3)	21 (0.2)	8956 (99.8)		10 (0.1)	8967 (99.9)	
Surgery				0.939			0.512
Yes	6637 (63.3)	16 (0.2)	6621 (99.8)		9 (0.1)	6628 (99.9)	

No	3855 (36.7)	9 (0.2)	3848 (99.8)	3 (0.1)	3852 (99.9)	
Hospitalization				0.561		0.653
Yes	8456 (80.6)	19 (0.2)	8437 (99.8)	10 (0.1)	8446 (99.9)	
No	2036 (19.4)	6 (0.3)	2030 (99.7)	2 (0.1)	2034 (99.9)	
Transfusion				0.703		0.970
Yes	1001 (9.5)	4 (0.4)	997 (99.6)	1 (0.1)	1000 (99.9)	
No	9395 (89.5)	21 (0.2)	9374 (99.8)	11 (0.1)	9384 ()	
Not know	95 (0.9)	0 (0)	95 (100)	0 (0)	95 (100)	
Genital aphthous				0.732		0.828
Yes	130 (1.2)	0 (0)	130 (100)	0 (0)	130 (100)	
No	10362 (98.8)	25 (0.2)	10337 (99.8)	12 (0.1)	10350 (99.9)	

Table 2. Comparison of blood and urine analysis based on HBV and HCV statuses.

variables	HBV			HCV		
	Positive	Negative	<i>P</i> <i>value</i>	Positive	Negative	<i>P</i> <i>value</i>
lood analysis						
WBC (/mm ³)	6.49±1.22	7.08±1.73	0.090	6.13±2.27	7.08±1.73	0.058
RBC (×1000/mm ³)	4.89±0.47	4.90±0.56	0.969	4.65±0.65	4.90±0.55	0.125
Hb (g/dL)	14.02±1.47	13.82±1.57	0.514	13.97±1.82	13.82±1.57	0.738
Hct (%)	41.95±3.72	41.33±4.15	0.459	41.05±4.71	41.33±4.14	0.812
MCV (fl)	86.20±8	84.88±7.57	0.384	88.88±8.66	84.87±7.56	0.066
MCH (pg)	28.82±3.27	28.39±3.05	0.481	30.23±3.42	28.39±3.05	0.036
MCHC (g/dL)	33.38±1	33.39±1.01	0.964	33.97±0.90	33.39±1.01	0.047
Platelet (/mm ³)	227.92±65.36	251.91±59.29	0.043	234.75±74.99	251.90±59.31	0.317
Lymphocyte (%)	36.07±7.12	38.71±9.23	0.269	36.09±9.42	38.71±9.22	0.394
Monocyte (%)	1.06±0.29	1.23±0.70	0.340	1.62±1.19	1.23±0.70	0.093
Granulocytes (%)	62.87±7.15	60.06±9.43	0.249	62.29±9.95	60.06±9.42	0.478
RDWCV (%)	12.01±0.50	12.57±0.98	0.023	12.75±1.58	12.57±0.98	0.550
RDWSD (fl)	41.51±3.88	42.29±3.48	0.374	45.93±9.90	42.27±3.45	0.273
Plateletcrit (×1000/	0.21±0.05	0.21±0.05	0.831	0.19±0.06	0.21±0.05	0.198
b)						
MPV (fl)	8.23±0.51	8.16±0.71	0.706	8.41±0.69	8.16±0.71	0.274
PDW (fl)	16.23±1.59	16.70±1.04	0.072	16.88±1.12	16.70±1.04	0.574
Glucose (mg/dL)	102.28±52.78	104.57±37.14	0.758	95.58±13.73	104.58±37.22	0.402
BUN (mg/dL)	14.10±4.09	13.37±3.53	0.304	14.93±5.65	13.37±3.50	0.123
Creatinine (mg/dL)	0.95±0.15	0.89±0.17	0.084	0.98±0.25	0.89±0.16	0.060
Triglyceride (mg/dL)	149.12±236.54	160.31±102.79	0.815	102.25±42.39	160.37±103.37	0.052
Cholesterol (mg/dL)	176.20±32.35	192.85±38.98	0.033	172.50±26.75	192.86±38.97	0.070
HDL (mg/dL)	49.20±10.25	48.39±10.99	0.711	59.58±16.59	48.38±10.97	0.039
LDL (mg/dL)	99.88±25.21	112.88±32.07	0.043	92.50±22.20	112.89±32.05	0.028
LDL:HDL	2.06±0.52	2.42±0.79	0.002	1.67±0.62	2.42±0.79	0.001
AST (IU/L)	19.20±7.82	19.06±8.43	0.935	46.58±39.00	19.02±8.25	0.032
ALT (IU/L)	15.72±8.26	18.82±13.54	0.253	38.25±27.10	18.77±13.43	0.030
ALP (IU/L)	194.00±52.32	207.03±59.88	0.277	215.75±55.11	206.98±59.89	0.612
GGT (IU/L)	18.37±6.40	25.05±20.80	0.108	59.17±73.63	25.00±20.62	0.136
Vit D ₃ (ng/ml)	25.01±14.88	21.77±12.39	0.201	26.94±13.97	21.77±12.40	0.149
rine analysis						
SG	1.02±0.01	15.18±119.12	0.552	1.02±0.01	15.18±119.14	0.680
pH	5.88±0.89	5.83±0.88	0.760	5.75±0.75	5.83±0.88	0.761
Creatinine (mg/dL)	134.17±71.03	140.36±77.30	0.749	136.43±79.52	140.36±77.32	0.872

Table 3. Serum level of HBV DNA and HCV RNA.

Serum levels of virus (copies/ml)	HBV DNA	HCV RNA
< 300 (below LOQ)	13 (52%)	0 (0)
< 10 ³	4 (16%)	0 (0)
10 ³ to < 10 ⁴	5 (20%)	0 (0)
10 ⁴ to < 10 ⁵	0 (0)	1 (8.3%)
10 ⁵ to < 10 ⁶	2 (8%)	7 (58.4%)
10 ⁶ to < 10 ⁷	0 (0)	3 (25%)
10 ⁷ to < 10 ⁸	1 (4%)	1 (8.3%)
≥ 10 ⁸	0 (0)	0 (0)
Total	25 (100)	12 (100)

LOQ: limit of quantification.

Figures

Figure 1

Geographic distribution of patients based on positivity of HBV and HCV and their gender. (The map depicted in figure is our own work)

Figure 2

Distribution of HCV genotype in our patients.