ISSN: 2474-3658

El-Ghitany and Farghaly. J Infect Dis Epidemiol 2019, 5:100
DOI: 10.23937/2474-3658/1510100
Volume 5 | Issue 6
Open Access

Journal of
Infectious Diseases and Epidemiology

RESEARCH ARTICLE

Host-Related Predictors of Persistence of Hepatitis C Virus Infection

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Abstract

Background: Spontaneous clearance occurs in varying proportions in individuals infected by hepatitis C virus (HCV). However, the factors associated with this clearance are debatable. Their recognition may lead to a better understanding of HCV natural history and eventually improve associated prediction and management models. Aim: This study was conducted to determine the host-related factors associated with persistence of HCV infection.

Methods: Among 1059 HCV-antibody-positive individuals who denied receiving HCV antiviral treatment, 257 (24.3%) spontaneously cleared the virus. Patient groups with persistent infection and clearance were compared in terms of potential HCV risk factors; host socio-demographic data, medical history, and behavioral factors. Results: Females (27.7%) and individuals below 45 years of age (31%) showed significantly higher clearance rates than males (20.3%) and older individuals (22.2%). Individuals who had a history of schistosomiasis and those who were receiving parenteral antischistosomal therapy had odds ratios (ORs) of 1.43 and 1.41 and confidence intervals of 1.08-1.9 and 1.06-1.87, p = 0.01 and 0.02 respectively. A history of incarceration was associated with a zero clearance rate. Low educational levels, high-risk occupations, frequent dentist visits, circumcision, and oral ulcers were associated with persistence of infection. Independent predictors associated with persistence of infection were frequent dentist visits, incarceration, fatigue, and jaundice (OR = 1.17, 3.67, 1.42, and 1.54, p = 0.04, 0.02, 0.03, 0.08 respectively), whereas the factor associated with clearance of infection was previous blood sampling (OR = 0.4).

Conclusion: The host-related predictors of HCV persistence of infection are related to either risk factors associated with repeated infection or symptoms of chronic infection, particularly fatigue with undetermined causes.

Keywords

Hepatitis C, Spontaneous clearance, Host-related factors

Background

Hepatitis C virus (HCV) infection is an escalating global health problem. It is endemic in many countries and imposes a growing burden on society and health-care systems [1]. HCV prevalence in the Eastern Mediterranean Region is heterogeneous, with at least 23 million people estimated to have HCV infection. The prevalence ranges from 1% to 2.5% in most countries [2], with higher prevalence reported in Egypt (10%) [3] and Libyan Arab Jamahiriya, Sudan, and Yemen (2.5%-10%) [4].

The natural course of HCV infection is highly variable and ranges from asymptomatic silent infection to fulminating liver disease usually occurring over decades [5]. Acute HCV is heralded by detectable HCV-RNA in serum, usually followed by an antibody response directed against various structural and nonstructural viral proteins [6]. Chronic HCV is marked by viral persistence for at least 6 months despite the presence of a humoral immune response. Recovery or spontaneous clearance is defined by the presence of HCV-specific antibodies (anti-HCV) in the absence of detectable HCV-RNA [7]. Published studies have estimated the proportion of spontaneous viral clearance to be 19.8%, 27.9%, 36.1%, and 37.1% within 3, 6, 12, and 24 months of the onset of infection, respectively [8].

Although the predictors of HCV clearance remain poorly elucidated, host-related factors including gender [8] and immune response [9] and viral factors such as HCV genotype and quasispecies diversity [10] appear to be relevant. Published findings suggest that previous HCV clearance can provide some protection against persistent reinfection [11]. Host genetics play an important role in HCV clearance, and the strongest

Citation: El-Ghitany EM, Farghaly AG (2019) Host-Related Predictors of Persistence of Hepatitis C Virus Infection. J Infect Dis Epidemiol 5:100. doi.org/10.23937/2474-3658/1510100

Accepted: November 14, 2019: **Published:** November 16, 2019

host-related factor associated with HCV clearance is favorable interleukin 28B gene polymorphism [12].

A major feature of HCV is the interindividual variability in the ability to clear the virus, either spontaneously or after treatment [13]. Knowledge of the variation between population subgroups in terms of the prevalence of spontaneous clearance could inform policy decisions on the use of direct-acting antivirals [8]. If individuals who will spontaneously clear the HCV infection can be identified beforehand, unnecessary antiviral treatment can be avoided and antiviral therapy can be promptly initiated to achieve a high sustained virologic response in those having a high risk of chronic HCV infection [14].

Egypt has the highest worldwide prevalence of HCV infection, and the prevalence rises steeply with age. Anti-HCV antibodies are detected in 2%-7% of children under the age of 10 years, approximately 10% of individuals between the ages of 10 and 20 years, and more than half of those between the ages of 40 and 50 years in rural areas in the Nile Delta region [15]. Although there have been advances in HCV treatment modalities, the therapeutic response is highly variable. Currently, no HCV vaccine is available; therefore, it is critical to identify the factors associated with spontaneous resolution or viral clearance in infected individuals. An improved understanding of the predictors of spontaneous clearance is required to guide public health strategies for HCV control at both the prevention and therapy levels [16].

Therefore, the present study is aimed at estimating the frequency and distribution of HCV spontaneous clearance rates and defining some host-related factors prevailing in Egypt.

Methods

Data collection and study population

An HCV cross-sectional survey study covering most Egyptian governorates was considered [17]. From the study cases, a simple random sample of anti-HCV positive cases was selected to study some host-factors related to the persistence of infection. For the current research, the sample size was calculated to be 482 using a 95% two-sided significance level and 90% power. All the data pertaining to anti-HCV positive individuals were collected in a single file for further computerized random sampling in the current research. The inclusion criteria were as follows: Anti-HCV positive individuals, at least 18-years-old, and had consented to participate. The exclusion criteria were as follows: Individuals who were currently receiving or had previously received HCV treatment, whose data were incomplete, or who refused to participate. The participants were interviewed by a trained interviewer using a standardized questionnaire [18], which comprised inquiries about socio-demographic data, medical history, and behavioral, environmental, or other factors that could contribute to the acquisition of HCV infection.

Laboratory analysis

All the individuals included in this study showed confirmed serologic evidence of positive HCV antibodies. Anti-HCV detection in serum was carried out using a commercial enzyme-linked immunosorbent assay (third-generation ELISA kit; DIALAB1, Austria). A second serum sample was retested using another ELISA kit (DiaSorin Murex 1, version 4.0, Italy) for confirmation. All the blood samples were tested for viremia using quantitative real-time polymerase chain reaction (PCR).

Definitions

Clearance of infection was defined as the presence of serologic evidence of HCV infection (confirmed positive HCV-Ab results) in the absence of viremia (negative PCR results). On the other hand, persistence of infection was defined as the presence of viremia in HCV serological positive cases (positive HCV-Ab and positive PCR results).

Statistical analysis

Data were revised, entered, and analyzed using the statistical software SPSS IBM version 20. All the statistical analyses were carried out using two-tailed tests and an alpha error of 0.05. The rates of spontaneous clearance and persistence of infection were calculated as the percentage of PCR-negative and PCR-positive individuals in the total population, respectively. Descriptive statistics in the form of frequencies and percentages were used to describe categorical data. The range, mean, and standard deviation were used to describe continuous data. Pearson chi-square tests were performed to examine the association between the studied factors and the rate of HCV clearance. Data were cross-tabulated against the dependent binary variable, i.e., PCR results. To examine the association between the studied factors and HCV-PCR positive status in the bivariate analysis, the odds ratio (OR) and 95% confidence interval (CI) were computed. A multivariate stepwise logistic regression model was created, and 22 factors were included regardless of their significance in the univariate analysis using a backward stepwise method.

Ethical statement

The present study was approved by the ethics committee of the High Institute of Public Health, Alexandria University (Egypt). The research strictly followed the ethical guidelines of the Declaration of Helsinki (2013) and the guidelines for Good Clinical Practice of the International Conference on Harmonization. Informed written consent was obtained from all the invited participants after the study aim and concerns

Table 1: Demographic distribution of the recruited HCV seropositive Egyptian population during the survey.

Demographic factors	No.	%
Sex		
Female	567	53.54
Male	492	46.46
Age in years		
< 45	248	23.42
45+	811	76.58
Mean ± SD	49.4 ± 11.31	
Range	18-75	
Residence		
Urban	222	20.96
Rural	837	79.04
Governorate		
Asyut	46	4.34
Beheira	149	14.07
Beni Suef	76	7.18
Cairo	18	1.69
Damietta	31	2.93
Faiyum	56	5.29
Giza	39	3.68
Ismailia	26	2.46
Marsa Matruh	55	5.19
Menoufeya	137	12.94
Minya	134	12.65
Port Said	4	0.38
Qalubeya	80	7.55
Sharqeya	96	9.07
Sohag	79	7.46
Suez	33	3.12
Total	1059	100.0

were explained to them. Data anonymity and confidentiality were maintained throughout the study.

Results

The total number of subjects included in this study was expanded to 1059 HCV-Ab-positive individuals recruited from 16 different governorates (Table 1); among these individuals, 79% were living in rural areas. Their ages ranged between 18 and 75 years with a mean age of 49.4. Females constituted 53.5% of the studied population.

The number of individuals who were PCR negative was 257; thus, the rates of spontaneous clearance and persistence of infection were 24.3% and 75.7%, respectively. The rate of spontaneous clearance was significantly higher among females (27.7% vs. 20.3% among males), individuals below 45 years of age (31% vs. 22.2% among those above 45 years of age), individuals educated up to the university level or higher (41.6% vs. 17.9% among illiterates), individuals engaged in low-risk occupations (26.6% vs. 13% among those engaged in high-risk occupations), individuals who never had oral ulcers (28.3% vs. 17.8% among those with a history of oral ulcers), and individuals who had not experienced unexplained fatigue during the last 6 months (27.3% vs. 19.7% among those who had experienced unexplained fatigue during the last 6 months). The results of univariate and multivariate analysis of host-related factors associated with HCV persistence of infection are listed in Table 2 and Table 3, respectively.

The independent factors that increased the probability of HCV persistence were a history of incarceration

Table 2: Host-related predictors of persistence of hepatitis C virus infection in the Egyptian population obtained by univariate analysis.

Host risk factor		Spontaneous cure n = 257		Persistent infection n = 802		Crude OR	95% CI	p-value
		No	%	No	%			
Gender	Female®	157	27.7	410	72.3	1.50	(1.13-2.00)	0.01
	Male	100	20.3	392	79.7			
Age	<45®	77	31.0	171	69.0	1.58	(1.15-2.16)	0.00
	45+	180	22.2	631	77.8			
Residence	Urban®	55	24.8	167	75.2	1.04	(0.73-1.46)	0.84
	Rural	202	24.3	635	75.7			
Education	Illiterate/able to read and write	133	17.9	610	82.1	3.26	(2.00-5.33)	0.00
	Basic	24	23.1	80	76.9	2.37	(1.25-4.51)	0.01
	Secondary	68	31.6	147	68.4	1.54	(0.90-2.63)	0.12
	University degree or higher®	32	41.6	45	58.4	-	-	-
Marital status	Never married®	4	28.6	10	71.4	1.25	(0.39-4.03)	0.71
	Ever married	253	24.2	792	75.8			

Risk of occupation	No®	233	26.6	642	73.4	2.42	(1.54-3.81)	0.00
	Yes	24	13.0	160	87.0			
Experience working abroad	No®	204	23.8	652	76.2	0.89	(0.62-1.26)	0.50
	Yes	53	26.1	150	73.9			
Tattooing	No®	245	24.6	751	75.4	1.39	(0.73-2.64)	0.32
	Yes	12	19.0	51	81.0			
Ear/body piercing	No®	161	25.5	471	74.5	1.18	(0.88-1.57)	0.27
	Yes	96	22.5	331	77.5			
Sharing sharp instruments	No®	59	22.3	205	77.7	0.87	(0.62-1.21)	0.40
	Yes	198	24.9	597	75.1			
Using barber tools	No®	102	23.0	341	77.0	0.89	(0.67-1.18)	0.42
	Yes	155	25.2	461	74.8			
Pierced with blood-contaminated tool	No®	238	24.5	732	75.5	1.20	(0.71-2.03)	0.50
	Yes	19	21.3	70	78.7			
Being bitten by an animal	No®	205	24.1	646	75.9	0.95	(0.67-1.35)	0.78
	Yes	52	25.0	156	75.0			
Exposed to blood	No®	197	24.1	622	75.9	0.95	(0.68-1.33)	0.76
	Yes	60	25.0	180	75.0			
Blood/blood product transfusion	No®	221	24.7	675	75.3	1.16	(0.77-1.72)	0.48
	Yes	36	22.1	127	77.9			
Invasive procedure	No®	174	23.5	565	76.5	0.88	(0.65-1.19)	0.40
	Yes	83	25.9	237	74.1			
Acupuncture	No®	245	23.5	797	76.5	0.13	(0.04-0.37)	0.00
	Yes	12	70.6	5	29.4			
History of jaundice	No®	236	24.4	732	75.6	1.07	(0.65-1.80)	0.78
	Yes	21	23.1	70	76.9			
Circumcision	No®	44	41.1	63	58.9	2.42	(1.60-3.67)	0.00
	Yes	213	22.4	739	77.6			
Blood sampling	No®	25	20.5	97	79.5	0.78	(0.49-1.25)	0.30
	Yes	232	24.8	705	75.2			
Frequent dentist visits	No®	118	29.0	289	71.0	1.51	(1.13-2.00)	0.00
	Yes	139	21.3	513	78.7			
Previous hospitalization	No®	128	23.5	417	76.5	0.92	(0.69-1.21)	0.54
	Yes	129	25.1	385	74.9			
Delivery at home	No®	150	22.6	515	77.4	0.78	(0.59-1.04)	0.09
	Yes	107	27.2	287	72.8			
Schistosomiasis	No®	123	28.2	313	71.8	1.43	(1.08-1.90)	0.01
	Yes	134	21.5	489	78.5			
PAT	No®	153	27.2	410	72.8	1.41	(1.06-1.87)	0.02
	Yes	104	21.0	392	79.0			
Genital ulcers	No®	181	24.0	574	76.0	0.95	(0.69-1.29)	0.72
	Yes	76	25.0	228	75.0			
History of oral ulcers	No®	185	28.3	469	71.7	1.82	(1.34-2.48)	0.00
	Yes	72	17.8	333	82.2			
Incarceration	No®	257	24.8	781	75.2	14.17	(0.86-234.73)	0.06
	Yes	0	0.0	21	100.0			
Previous stay at camps/youth homes	No®	141	21.5	515	78.5	0.68	(0.51-0.90)	0.01
	Yes	116	28.8	287	71.2			
Fatigue during the last 6 months	No®	174	27.3	463	72.7	1.53	(1.14-2.07)	0.00
	Yes	83	19.7	339	80.3			

Opioid injections	No®	251	24.0	793	76.0	0.47	(0.17-1.35)	0.16
	Yes	6	40.0	9	60.0			
Alcohol consumption	No®	241	24.3	749	75.7	1.07	(0.60-1.90)	0.83
	Yes	16	23.2	53	76.8			
Shisha smoking	No®	213	25.4	627	74.6	1.35	(0.94-1.95)	0.11
	Yes	44	20.1	175	79.9			
Family history of hepatic disease	No®	209	23.9	666	76.1	0.90	(0.62-1.28)	0.53
	Yes	48	26.1	136	73.9			
Partner with STIs	No®	241	23.6	780	76.4	0.42	(0.22-0.82)	0.01
	Yes	16	42.1	22	57.9			
Partner infected with HCV	No®	249	24.9	751	75.1	2.11	(0.99-4.52)	0.05
	Yes	8	13.6	51	86.4			
Contact with jaundiced person	No®	239	25.0	716	75.0	1.59	(0.94-2.71)	0.08
	Yes	18	17.3	86	82.7			
Sex during menstruation	No®	248	24.6	762	75.4	1.45	(0.69-3.02)	0.33
	Yes	9	18.4	40	81.6			

PAT: Parenteral antischistosomal therapy; STIs: Sexually transmitted infections; ®: Reference category.

Table 3: Independent host-related predictors of persistence of hepatitis C virus infection in the Egyptian population obtained by logistic regression analysis.

Independent factor	Adjusted OR	95% CI	p-value
History of jaundice	1.54	(0.95-2.49)	0.08
Blood sampling	0.4	(0.19-0.87)	0.02
Frequent dentist visits	1.17	(1.08-1.26)	0.04
Incarceration	3.67	(1.24-10.85)	0.02
Fatigue during the last 6 months	1.42	(1.03-1.95)	0.03

(OR = 3.67, CI = 1.24-10.85), jaundice (OR = 1.54, CI = 0.95-2.49), unexplained fatigue during the last 6 months (OR = 1.42, CI = 1.03-1.95), and frequent dentist visits (OR = 1.17, CI = 1.08-1.26). The factor associated with a lower risk of persistent infection was previous blood sampling (OR = 0.4, CI = 0.19-0.87).

Discussion

This study aimed to detect the frequency of spontaneous clearance of HCV in Egypt and determine the host-related predictors of persistence of HCV. The results revealed that out of 1059 anti-HCV positive individuals (who denied receiving HCV antiviral treatment), 257 (24.3%) spontaneously cleared the virus (negative RNA). This finding matched previous results that indicated that on average, the recovery rate concerning acute HCV infection was close to 20% [19]. Similarly, published data pertaining to a population at risk of exposure indicated that 14%-40% of the people infected with HCV spontaneously cleared the virus [20]. Other studies reported even higher rates of at least 50% spontaneous clearance of HCV in various populations [21]. Seeff and Hoofnagle [22] reported that the rates of clearance differed according to the type of study, duration of follow up, and population selected for the study.

The rate of spontaneous clearance of HCV-RNA could be underestimated or overestimated because of infrequent repeated RNA testing. It was found that HCV-RNA might be transiently undetectable in an infected patient even when the virus is still present in the liver and peripheral blood mononuclear cells [23]. Nevertheless, Takaki, et al. [24] indicated that humoral immunity might be progressively lost in patients who had recovered from HCV infection spontaneously.

Several epidemiologic studies have tried to identify the host-related factors determining spontaneous clearance with respect to the factors determining viral persistence, but the results have often been conflicting [25]. In the present research, younger participants (< 45 years) had a significantly higher rate of viral clearance than the older participants (> 45 years) (31% vs. 22.2%, respectively). The above results are supported by the results of many published reports, which found that young age was one of the host-related factors associated with spontaneous clearance of HCV infection [26] probably because younger people have a more vigorous immune response to viral infection [27].

In the present study, female participants cleared the virus spontaneously more frequently than males (27.7% vs. 20.3%, respectively), which is similar to the observations made in other studies [21]. Esmat, et al.

[28] even recommended that female children should be given the opportunity to clear their infection. This variation might be due to the larger effect of the IL28B and HCV genotypes on viral clearance among females than among males or due to a gender difference in immunity [10]. There is considerable evidence that suggests that sex hormones influence immunity [8], and the estrogen receptor alpha ESR2rs4986938AA genotype was found to be strongly associated with HCV clearance among the Chinese population [29].

The effect of coinfection, particularly with hepatitis B virus (HBV) and *Schistosoma*, on HCV clearance is a matter of debate [30]. In the current study, only schistosomiasis coinfection was studied, and the results showed a 43% increase in the risk of persistence of infection. Some studies found that *Schistosoma* infection had no negative effect on HCV-specific cell-mediated immunity [31] and eventually no influence on viral clearance [28]. However, other studies found that the infection had a significant effect on host immune reactions including cytokine patterns and cytotoxic T lymphocyte responses [32]; the case of coinfection resulted in a diminished virus clearance capacity, a higher viral load, greater morbidity and mortality, and failure to treatment [33] in comparison to the case of HCV infection alone.

A history of acute icteric hepatitis after inoculation has been frequently demonstrated to be associated with spontaneous viral clearance. It is speculated that persons with a strong basal immune response are likely to contract jaundice and hence have a better likelihood of eradicating the HCV and controlling the infection [34]. In contrast, a positive history of jaundice among our participants was one of the independent predictors for the persistence of HCV infection (OR = 1.54). In the present study, the history of jaundice is not necessarily a symptom in the case of acute infection, but jaundice is most probably due to liver insult late in the course of the disease or less probably a symptom of hepatitis A infection, which is endemic in Egypt.

Other independent predictors for persistent HCV were elicited from our work. These were a positive history of fatigue (OR = 1.42), dental manipulation (OR = 1.17), and incarceration (OR = 3.67). The above findings matched well with those documented by El-Attar, et al. [19], who found that the symptoms of fatigue, bleeding, and epistaxis were more common in subjects who did not clear the infection. Similarly, Hoofnagle [35] concluded that most patients with persistent HCV infection showed a few common symptoms, with the most common being fatigue.

The transmission mode is also thought to be an important factor in predicting the outcome of HCV infection [36]. Based on a study among Egyptian children, Esmat, et al. [28] found that dental interventions were more likely to expose the patient to a high viral dose and thereby result in a chronic persistent infection. The above justification is supported by the results of the present work as well as other study [37].

Published data support the strategy of starting early treatment for high-risk groups that are less likely to achieve spontaneous clearance because these groups pose a higher risk of transmitting the virus to the community and may be more likely to be missed in follow-ups [8]. In the present research, incarceration was one of the four main independent factors significantly associated with the persistence of HCV infection. The significant association of a positive history of incarceration with HCV persistence could be attributed to risky behavior such as drug abuse, alcohol consumption, smoking, and abnormal sexual practices, which make the inmates vulnerable to chronic and communicable diseases. Moreover, inmates suffer from poor nutrition and lack of preventive care [38]. Intravenous drug abusers were considered to be a risk group that was less likely to achieve spontaneous clearance of HCV infection. Accordingly, intravenous drug abuse was reported to be negatively associated with spontaneous clearance of HCV [8]. This group-and other similar groups vulnerable to repeated exposures-does clear the virus but is reinfected with distinct HCV strains, which could have a significant effect on immune functions, thereby hindering spontaneous clearance.

Unlike in other studies, in this study, neither alcohol consumption nor tobacco and cannabis smoking demonstrated significant risks for viral persistence. These factors were reported to have several immunosuppressive effects and were found to lead to persistent infection because of an increase in fibrosis in patients with chronic HCV infection [39,40].

Conclusion

In Egypt, HCV spontaneous clearance occurs at a rate of 24.3%. Females and young individuals (< 45 years) have higher clearance rates. Host-related predictors of HCV persistence of infection are related to either risk factors associated with repeated infection (parenteral antischistosomal therapy, frequent dentist visits, high-risk occupations, and incarceration) or symptoms of chronic infection, particularly jaundice and fatigue with undetermined causes.

Limitations

The original survey for which we recruited the participants was a community-based cross-sectional multicenter study. Therefore, it was not feasible to carry out follow-ups with the participants 6 months later to ensure persistence using PCR. However, this drawback was compensated by increasing the sample size and its power, particularly considering that HCV is a silent disease wherein the acute infection is very hard to detect in both clinical and research settings unless a longitudi-

nal study spanning many decades is conducted.

Viral and genetic factors were not analyzed in this study because of budget constraints.

Acknowledgment

This work was financially supported by the Science and Technology Development Fund (STDF), Egypt (Grant No. 3469).

Conflict of Interest

Nothing to declare.

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