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Factors Associated with Positive Predictability of the Anti-HCV ELISA Method with Confirmatory RT-PCR

The positive predictability of anti-HCV ELISA is low, especially, in blood donors and in healthy populations. False positive anti-HCV results pose some difficulties in medical practice and in blood screening. The aim of this study was to identify the factors associated with true hepatitis C virus (HCV) infection among anti-HCV ELISA-positives. A case-control analysis was conducted using 354 subjects who were positive for anti-HCV ELISA. All subjects were tested for true HCV infection using the reverse transcriptase polymerase chain reaction (RT-PCR). Tests for serum alanine aminotransferase (ALT), fasting glucose, HBsAg, anti-HBc antibody, alpha-fetoprotein, platelet count and ultrasound of liver were also performed. Epidemiological data were obtained by self-administered questionnaires. Out of 354 subjects, 202 (57.1%) were positive for HCV by RT-PCR and 152 were negative and used as the control group. In multivariate analysis, blood transfusion (odds ratio, OR 2.3, 95% confidence interval, CI 1.3-4.0), elevated ALT (OR 2.2, 95% CI 1.2-4.3) and higher anti-HCV ELISA ratios (more than 3; OR 1.7, 95% CI 1.3-2.1) were associated with true HCV infection. Thrombocytopenia was also associated with the presence of HCV in univariate analysis. These results suggest that a history of blood transfusion, elevated ALT and a high score on anti-HCV ELISA ratios are associated with true HCV infection among anti-HCV ELISA-positives.

Key Words: *Hepatitis C-like virus; Hepatitis C antibodies; Enzyme-linked immunosorbent assay; Reverse transcriptase polymerase chain reaction; Risk factors*

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INTRODUCTION

In Korea, blood donors and patients with liver disease have been systematically tested for hepatitis C virus antibody (anti-HCV) with an enzyme linked immuno-absorbent assay (ELISA) since 1990. Several studies have reported the anti-HCV ELISA test to have low specificity and low positive predictive values, especially in blood donors and low risk groups (1, 2). This false positivity might be a source of overestimated prevalence of HCV infection and nullifying effects of risk factors. Therefore, knowing about the factors associated with true HCV infection among anti-HCV ELISA-positive cases would be very helpful to physicians for decision-making on further diagnostic and medication procedures. Reverse transcriptase polymerase chain reaction (RT-PCR) is an appropriate method for confirming true HCV infection. However, it is an expensive and sophisticated method in clinical practice.

This study was conducted to identify the factors associated with positive predictability of anti-HCV ELISA method with confirmatory RT-PCR, and to propose data helpful for clinical practice and future research.

MATERIALS AND METHODS

Study population

The subjects were anti-HCV ELISA positive cases who underwent a periodic health examination between September 1993 and December 1996 at the Asan Medical Center in Seoul, Korea. Asan Medical Center is a private university-based tertiary medical institution primarily serving residents of Seoul. By November 1997, 354 (58.8%) out of 602 subjects, to whom mailed a letter inviting to participate the study, responded and consented to participate in the study. Using a structured questionnaire, participants were asked about their past medical history including surgical and dental procedures, blood transfusions, needle sharing, jaundice, acupuncture, endoscopy, tattoos, and ear piercing. And, with ALT and

abdominal sonogram, RT-PCR was performed to confirm the status of true HCV infection. Out of the 354 patients, 202 (57.1%) were found to be infected with HCV using RT-PCR (PCR-positive). The remaining 152 (42.9 %) were not found to be infected (PCR-negative). Demographic characteristics were similar between the two groups (Table 1). Informed consent was obtained from each subject prior to collection of blood samples.

Laboratory tests

All the participants were screened with a second generation anti-HCV ELISA (Abbott Laboratories) at each visit. The ELISA ratio was calculated by signal to cutoff (s/c) ratio under the guidance of Abbott Laboratories (2). Anti-HCV ELISA was considered positive when the ELISA ratio was greater than 1.0. ALT activity was considered elevated when the value was greater than 40 IU/L. To detect hepatitis C viral sequences, serum RNA was extracted, reverse transcribed, and amplified using the nested PCR method (3). The participants were also tested for HBsAg and anti-HBc (by radioimmunoassay, Abbott), alpha-fetoprotein, fasting glucose and platelet count. Alpha-fetoprotein was considered elevated when the value was greater than 20 ng/mL.

Table 1. Demographic characteristics among 354 anti-HCV ELISA-positive patients according to RT-PCR results

Characteristics	PCR-positive		PCR-negative	
	No.	(%)	No.	(%)
Total	202	(100.0)	152	(100.0)
Gender				
Male	116	(57.4)	88	(57.9)
Female	86	(42.6)	64	(42.1)
Age				
<40	19	(9.4)	23	(15.1)
40-49	40	(19.8)	24	(15.8)
50-59	66	(32.7)	55	(36.2)
≥60	77	(38.1)	50	(32.9)
Marital status				
Married	187	(96.9)	135	(93.8)
Never married	6	(3.1)	9	(6.2)
Years of education				
<12	53	(27.7)	35	(24.3)
12	50	(26.2)	39	(27.1)
>12	88	(46.1)	70	(48.6)
Income/Month				
<1 mill*	41	(23.2)	19	(13.8)
1-3	98	(55.4)	81	(58.7)
>3	38	(21.5)	38	(27.5)
Smoking				
Current smoker	43	(22.4)	34	(23.8)
Non-smoker	149	(77.6)	109	(76.2)
Alcohol				
Drinker	74	(38.5)	65	(45.1)
Non-drinker	118	(61.5)	79	(54.9)

*million Korean won

Statistical analysis

The association of possible factors influencing true HCV infection, in terms of PCR-positivity among anti-HCV ELISA-positives, was assessed using odds ratios. The χ^2 test or Fisher's exact test were used to determine the statistical significance of the odds ratios. Factors significant in univariate analyses ($p<0.05$) were examined after being stratified by possible confounders, using the Mantel Haenszel method. Multiple logistic regression analysis was also employed to determine whether the observed associations were independent of other factors.

RESULTS

Positive predictive value of the anti-HCV ELISA method

Out of the 354 anti-HCV ELISA-positive cases, 202 were found to be infected with HCV using the RT-PCR method. The positive predictive value of anti-HCV ELISA was estimated as 57.1%.

Clinical diagnoses of the study subjects

Among the 202 PCR-positive cases, we found 102 cases of elevated ALT, 83 of normal liver function, 15 of cirrhosis and two of hepatocellular carcinoma. Among the 152 PCR-negative cases, we found 39 cases of elevated ALT, 109 of normal liver function and four of cirrhosis (Table 2).

Univariate analysis of the factors for true HCV infection

A history of blood transfusion (OR 2.5, 95% CI 1.5-4.2), and of surgical (OR 1.6, 95% CI 1.0-2.5) or dental procedure (OR 1.8, 95% CI 1.1-2.8) was associated with

Table 2. Clinical diagnoses of 354 anti-HCV ELISA-positive patients according to RT-PCR results

Characteristics	PCR-positive		PCR-negative	
	No.	(%)	No.	(%)
Total	202	(100.0)	152	(100.0)
Normal ALT*	83	(41.1)	109	(71.7)
Elevated ALT	102	(50.5)	39	(25.7)
Cirrhosis	15	(7.4)	4	(2.6)
Hepatocellular carcinoma	2	(1.0)	0	(0.0)

*Alanine aminotransferase

an increased risk of PCR-positivity, that means true HCV infection. In this study, other possible factors such as needle sharing, endoscopy, acupuncture, tattooing, ear piercing, hemodialysis, sexually transmitted disease, a history of jaundice or a family history of hepatitis were not found to be associated with an increased risk of true HCV infection. Homosexuality could not be evaluated since no homosexual patients were found among the PCR-negative cases (Table 3).

Among the laboratory data elevated serum ALT (OR 3.6, 95% CI 2.3-5.7), an anti-HCV ELISA ratio of 3.0 or higher (OR 8.5, 95% CI 4.3-16.8), thrombocytopenia (OR 2.7, 95% CI 1.4-5.4) and the repeated positive result of anti-HCV (OR 5.7, 95% CI 2.1-15.6) were all associated with an increased risk of true HCV infection. An overall increase in the tendency of HCV infection with an anti-HCV ELISA ratio was observed. Other laboratory findings such as HBsAg, anti-HBc, alpha-fetoprotein, hypergylcemia, and splenomegaly were not found to be associated with an increased risk of true HCV infection (Table 4).

Multivariate analysis of the factors for true HCV infection

Table 5 shows the results of multivariate analysis of the possible risk factors for hepatitis C virus infection.

Table 3. Univariate analysis of potential risk factors for PCR-positivity among 354 anti-HCV ELISA-positives

Characteristics	PCR-positive		PCR-negative		OR	95% CI
	No.	(%)	No.	(%)		
Total	202	(100.0)	152	(100.0)		
Surgical procedure						
Yes	104	(53.3)	63	(41.7)	1.60	(1.04-2.45)
No	91	(46.7)	88	(58.3)		
Blood transfusion						
Yes	70	(37.2)	27	(19.3)	2.48	(1.49-4.15)
No	118	(62.8)	113	(80.7)		
Needle sharing						
Yes	9	(5.1)	3	(2.1)	2.51	(0.67-9.46)
No	166	(94.9)	139	(97.9)		
Endoscopy						
Yes	136	(70.1)	100	(69.0)	1.06	(0.66-1.68)
No	58	(29.9)	45	(31.0)		
Dental procedure						
Yes	133	(71.9)	83	(58.9)	1.79	(1.12-2.84)
No	52	(28.1)	58	(41.1)		
Acupuncture						
Yes	144	(75.0)	115	(77.2)	0.89	(0.54-1.47)
No	48	(25.0)	34	(22.8)		
Tattooing						
Yes	30	(16.0)	20	(13.9)	1.18	(0.64-2.17)
No	158	(84.0)	124	(86.1)		
Ear piercing						
Yes	36	(19.0)	21	(14.7)	1.36	(0.76-2.45)
No	154	(81.0)	122	(85.3)		
History of hemodialysis						
Yes	1	(2.4)	2	(2.5)	0.96	(0.09-10.94)
No	40	(97.6)	77	(97.5)		
History of STD*						
Yes	43	(23.4)	36	(25.9)	0.87	(0.52-1.45)
No	141	(76.6)	103	(74.1)		
History of jaundice						
Yes	43	(23.1)	31	(21.7)	1.09	(0.64-1.83)
No	143	(76.9)	112	(78.3)		
Family history of hepatitis						
Yes	38	(20.5)	36	(24.8)	0.78	(0.47-1.32)
No	147	(79.5)	109	(75.2)		

*Sexually transmitted disease

Table 4. Univariate analysis of laboratory data for PCR-positivity among 354 anti-HCV ELISA-positives

Characteristics	PCR-positive		PCR-negative		OR	95% CI	*p*
	No.	(%)	No.	(%)			
Total	202	(100.0)	152	(100.0)			
Serum ALT							
Normal	83	(41.1)	109	(71.7)	1.0		
Elevated	119	(58.9)	43	(28.3)	3.63	(2.32-5.70)	0.001
Anti-HCV ELISA ratio							
1.0-1.9	13	(7.5)	48	(36.1)	1.0		
2.0-2.9	12	(6.9)	21	(15.8)	2.11	(0.83-5.39)	
3.0-3.9	15	(8.7)	12	(9.0)	4.62	(1.74-12.24)	0.001*
4.0-4.9	84	(48.6)	27	(20.3)	11.49	(5.42-24.34)	
5.0≤	49	(28.3)	25	(18.8)	7.24	(3.32-15.78)	
HBsAg							
Negative	173	(94.5)	135	(95.1)	1.0		
Positive	10	(5.5)	7	(4.9)	1.12	(0.41-3.01)	0.830
Anti-HBc							
Negative	28	(21.9)	38	(30.6)	1.0		
Positive	100	(78.1)	86	(69.4)	1.58	(0.92-2.78)	0.113
α-fetoprotein							
Normal	160	(93.0)	123	(97.6)	1.0		
Increased	12	(7.1)	3	(2.4)	3.08	(0.85-11.14)	0.106
Thrombocytopenia (<130,000/μL)							
No	106	(75.2)	106	(89.1)	1.0		
Yes	35	(24.8)	13	(10.9)	2.69	(1.35-5.37)	0.004
Hyperglycemia (>140 mg%)							
No	151	(95.6)	112	(91.1)			
Yes	7	(4.4)	11	(8.9)	0.47	(0.18-1.26)	0.125
Splenomegaly by ultrasound							
No	161	(91.5)	129	(97.0)	1.0		
Yes	15	(8.5)	4	(3.0)	3.01	(0.97-9.27)	0.056
Repeated positivity of anti-HCV ELISA							
No	5	(2.5)	19	(12.7)	1.0		
Yes	196	(97.5)	131	(87.3)	5.69	(2.07-15.61)	0.001

*Mantel-Haenzsel test of trend

A history of blood transfusion was shown to be strongly related to the risk of HCV infection (OR 2.3, 95% CI 1.3-4.0). The association between undergoing a dental procedure and true HCV infection was of marginal statistical significance (OR 1.6, 95% CI 0.98-2.73). In this multivariate model, other factors such as gender, age and surgical procedure were not found to be associated with an increased risk of true HCV infection.

Elevated ALT was found to be strongly related to the risk of true HCV infection (OR 2.2, 95% CI 1.2-4.3). An anti-HCV ELISA ratio was also shown to be a possible factor (OR 1.7, 95% CI 1.3-2.1). In this multivariate model, other factors such as gender, age, thrombocytopenia and repeated anti-HCV positivity were not found to be associated with an increased risk of true HCV infection (Table 6).

Table 5. Multivariate analysis of risk factors for PCR-positivity among 354 anti-HCV ELISA-positives

Risk factors	Adjusted OR	95% CI	Adjusted *p*
Female	0.95	0.74-1.22	0.832
Age (10 yrs)	1.17	0.94-1.45	0.164
Surgical procedure	1.32	0.79-2.20	0.275
Blood transfusion	2.25	1.26-4.01	0.005
Dental procedure	1.63	0.98-2.73	0.056

Table 6. Multivariate analysis of laboratory data for PCR-positivity among 354 anti-HCV ELISA-positives

Laboratory factors	Adjusted OR	95% CI	Adjusted *p*
Female	1.10	0.59-2.04	0.757
Age (10 yrs)	0.89	0.66-1.20	0.452
Elevated ALT	2.22	1.15-4.25	0.015
Anti-HCV ELISA ratio	1.67	1.34-2.08	<0.001
Thrombocytopenia	1.68	0.75-3.73	0.197
Repeated positivity of anti-HCV ELISA	3.52	0.38-32.31	0.256

DISCUSSION

The overall positive predictive value of anti-HCV ELISA was 57% among our subjects, which is higher than that among blood donors (4). This may be due to the high prevalence of liver disease and high proportion of older age subjects in our study group.

This study shows the factors associated with true HCV infection among anti-HCV ELISA-positives. They are a history of blood transfusion, elevated ALT and a greater anti-HCV ELISA ratio. These factors accounted for approximately 28% of PCR-positives according to our logistic model. Our results provide important information regarding the screening of HCV infection for anti-viral therapy.

In our study transfusion, the classic form of parenteral transmission, is associated with an elevated odds ratio of 2.3. This is markedly lower than the odds ratio (12.6) calculated in our previous study (5), which compared PCR-positive cases to ELISA-negative healthy controls. This is due to the nullifying effect in the risk factor analysis of PCR-negativity in the anti-HCV ELISA-positive group. Even though the prevalence of acupuncture was high in this study population, it was not found to be a risk factor for HCV infection. This finding conflicts with the results of another study, which found acupuncture to be a route of transmission of HCV (6). A history of having been tattooed was also not found to be associated with an increased risk of HCV infection, which also conflicts with other studies (7, 8). Previous surgery was not associated with true HCV infection in this study, which is consistent with some (9, 10), but not all studies (11, 12). A history of undergoing a dental procedure was found to be of marginal significance in the multivariate analysis of risk factors, but these findings are also controversial (11-13). Certain well known parenteral risk factors, such as needle sharing and hemodialysis (12, 14), were also not found to be associated with the risk of HCV infection. These factors, however, could not be thoroughly evaluated because of the very low prevalence of intravenous drug use and hemodialysis in our population. Other risk factors for parenteral exposure, such as endoscopy and ear piercing, were not found to be associated with HCV infection.

A history of jaundice was not shown to be associated with HCV infection in this population, which is also inconsistent with other studies (7, 12). This is due to the same reason as the lower than expected association of transfusion. A history of sexually transmitted disease was not found to be a risk factor, again conflicting with the results of other studies (15-16). One study, however, has shown the absence of viral RNA in saliva, semen and vaginal secretion from the patients with HCV infection (17). Family history of hepatitis was not found to be associated with HCV infection in our study, consistent with other studies (18). In addition, our previous study (5) and others (19) reported the lack of familial clustering of HCV infection and a very low rate of sero-prevalence in family members of patients with HCV infection. We suggest, therefore, that non-parenteral transmission through sexual and other close contacts play only a minor role in the transmission of HCV.

We found ALT to be associated with HCV infection, as have other studies (12). Before 1989, elevated ALT and the presence anti-HBc antibodies were used as surrogate markers for non-A, non-B hepatitis in Europe and North America (20), areas known as non-endemic of hepatitis B. However, the presence of anti-HBc antibodies was not associated with true HCV infection in our population, where hepatitis B was endemic (21). The overall increasing tendency of HCV infection with an increasing anti-HCV ELISA ratio was observed in our study. Also, high ELISA ratios have shown an increased risk of true HCV infection in our study, as well as in others (2, 12). This suggests that more false positives occurred in anti-HCV ELISA-positive cases with a low ELISA ratio (<3.0) than in those with a high ELISA ratio (4). Thrombocytopenia was associated with an increased risk of HCV infection in univariate analysis, but not in multivariate analysis when controlling for confounding variables such as ALT activity and ELISA ratio. Another recent study demonstrated that chronic infection with HCV might produce a significant autoimmune reaction to platelets, leading to thrombocytopenia (22). Therefore, we suggest that examination of platelet count may be used as an indicator of HCV infection when ALT activity is normal in anti-HCV ELISA-positive patients. It deserves further study in the future. Splenomegaly, which indicates severe liver damage such as cirrhosis, was not found to be associated with true HCV infection. Therefore, we suggest that splenomegaly is not a good indicator of the presence of HCV-RNA in anti-HCV ELISA-positive patients.

The limitation of our study was that our study population was selected from a hospital-based sample. A community-based sample may have had a higher prevalence of drug abuse and other factors.

In summary, the factors associated with positive predictability of the anti-HCV ELISA method among anti-HCV ELISA-positive patients are a previous history of blood transfusion, elevated ALT and an anti-HCV ELISA ratio of three or greater.

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