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Risk Factors Associated with HCV among Opioid-dependent Patients in a Multisite Study

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Abstract

We examined risk factors associated with Hepatitis C virus (HCV) infection among opioid-dependent patients enrolled into medication-assisted therapy (buprenorphine or methadone) to determine factors affecting chronic infection. Patients (N=1,039) were randomized as part of a larger, multisite clinical trial sponsored by the National Drug Abuse Treatment Clinical Trials Network assessing liver function. HCV status was first assessed with an antibody screen; if positive, then current infection was determined with an antigen screen testing for detectable virus. Patients were classified as HCV negative, HCV positive but have cleared the virus, or as having chronic HCV. Logistic regression analysis was used to examine demographic and behavioral correlates of the three groups. Thirty-four percent of patients were classified with chronic infection and 14% had evidence of prior infection with apparent clearing of the virus. Chronic

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Compliance with Ethical Standards

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of Interest

Yih-Ing Hser received a small educational grant from Reckitt Benckiser Pharmaceuticals to support a Summer Institute on Promoting Recovery within the Changing Health Service System. Andrew Saxon has served as a speaker for Reckitt Benckiser Pharmaceuticals, is a Section Editor for UpToDate for which he receives royalties, and has served as a member of a scientific advisory board for Alkermes, Inc. Walter Ling has served as a consultant for Reckitt Benckiser Pharmaceuticals. No other financial or other possible conflicts of interest exist for authors.

infection was associated with recent injection drug use and cocaine use. Chronic HCV infection was also associated with being older and Hispanic. Age, ethnicity, and current drug use increase the likelihood of being chronically infected with HCV. Strategies targeting high risk subgroups can aid in preventing further disease escalation.

Keywords

hepatitis C; injection drug use; buprenorphine; methadone maintenance; injection risk behavior

Introduction

Hepatitis C virus (HCV) is the most common blood-borne viral infection in the United States, accounting for more disease and death than human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) [1, 2]. It is estimated that approximately 5.2 million people, roughly 2%, are living with HCV [3]. Of those exposed to the virus, approximately 80% will develop chronic HCV, a lasting infection that is generally asymptomatic for decades [2, 4]. Untreated chronic infection is associated with increased risk for cirrhosis and liver cancer, both of which are costly and life-threatening [5]. Thus, populations identified as being high risk for chronic infection provide valuable information regarding which factors are associated with increased risk so that prevention and services may better target regions and people exhibiting the greatest need.

Injection drug users (IDUs) who share needles and other drug use equipment are at highest risk of contracting HCV [1, 6]. Globally, 60–80% of IDUs are HCV positive [2]. Engaging in unsafe behaviors associated with addiction, such as higher risk sexual behaviors, is believed to contribute to the transmission of HCV as well as hepatitis B virus (HBV) and HIV [6–9]. Although research regarding the likelihood of contracting HCV through high risk sexual behavior alone is somewhat inconclusive, there is evidence that IDUs engaging in sexual relationships often share injecting equipment and practice poor sterilization procedures, thereby raising their risk for HBV, HCV, and HIV [10]. Furthermore, specific subgroups may be at greater risk than others for contracting HCV through sexual contact. Neaigus and colleagues [10] found that among men who had never shared injecting paraphernalia, having a greater number of lifetime sex partners was associated with being HCV seropositive. The authors attributed this finding to increased risk in men who have sex with men (MSM) and sex practices that may involve blood-to-blood transmission. Given the damaging effects of drugs and alcohol on liver health, identifying and treating those infected with one or more of these viruses are essential to providing optimal healthcare to drug users and to limiting the spread of HIV, HBV, and HCV within the community at large.

Among IDUs, risk for infection increases with certain drug use behaviors beyond that of sharing contaminated paraphernalia. Certain patterns of drug use have also been associated with greater likelihood of contracting HCV, such as injection of drugs other than heroin (i.e., prescription opioids and cocaine) [11, 12], and reporting more years and greater frequency of injection drug use [11, 13, 14]. A recent study [12] found that among a sample of out-of-treatment heroin users, those with heavier drinking and cocaine use were more likely to be

HCV-positive. More specifically, participants reporting cocaine injection within the past month had a ninefold greater risk to be infected than those with no cocaine use or with non-injection use. These findings highlight the need for targeting HCV prevention efforts alongside drug treatment for substances other than heroin.

Unfortunately, however, even patients considered to be highest risk (i.e., IDUs) often do not receive testing and/or treatment for HCV infection [15]. In fact, it is estimated that the annual treatment uptake among IDUs is only around 1–2% [16, 17]. Given the high risk of HCV-related morbidity and mortality among those identified with chronic HCV infection, greater accuracy in identifying currently infected persons is needed. A reactive HCV antibody test indicates that HCV infection has occurred but it does not distinguish between individuals with active infection and those who contracted the virus in the past but have spontaneously cleared the virus [18]. Thus, Centers for Disease Control and Prevention [19] recommend that additional screenings be in place for individuals with HCV seropositive antibody tests, particularly those in high risk groups. HCV antigen testing to determine detectable virus has been suggested as a stand-alone or antibody/antigen combination screen to identify active infection [20]. As a stand-alone, antigen screening can detect HCV infection up to 50 days prior to seroconversion, thereby closing the “window period” before HCV antibodies develop and indicating acute infection [21, 22]. Chronic infection is indicated when antigen screening is conducted in combination with antibody testing and both tests yield positive results.

Although previous studies have relied on a singular HCV antibody screen to determine infection status, the current study more closely adheres to newer CDC [19] guidelines by using both antibody and antigen screening. As described above, the combination screening allows for greater accuracy in identifying individuals with active, non-resolved cases of HCV infection. This distinction is important in determining appropriate receipt of preventive services and medical treatment, especially among those whose history of substance abuse places them at increased risk for liver-related illnesses. The current study highlights the importance of detecting risks involved in current HCV infection among IDUs in order to inform best practices for testing and monitoring.

2. Methods

2.1 Participants

The present analysis includes 1,039 opioid-dependent participants whose HCV serostatus was assessed as part of a larger clinical trial. Sponsored by the National Drug Abuse Treatment Clinical Trials Network, the original study was a multisite, open-label, phase IV study to assess liver function in participants randomized to medication condition (BUP [given in the form of buprenorphine/naloxone], MET [methadone]) [23]. A total of 1,269 eligible patients from 9 federally licensed opioid treatment programs across the U.S. were randomized (within site) and inducted on study medication (BUP = 740, MET = 529) from 2006 to 2009. The unequal sample sizes in the two conditions occurred as a consequence of efforts to achieve target sample sizes of 300 for each medication. The initial randomization scheme of 1:1 (BUP:MET) was changed to 2:1 in December 2007 (18 months after

initiation) due to the higher dropout in the BUP condition. The present study focused on 1,039 patients for whom HCV serostatus was collected.

Baseline comparisons indicate some significant differences between those tested for HCV (n=1039) and not tested (n=228). Specifically, participants without available HCV data were significantly more likely to be in the BUP treatment group (71.5% vs. 55.4%, $p < .0001$), to live on the west coast (80.7% vs. 66.5%, $p < .0001$), and to have tested positive for amphetamines at baseline (13.2% vs. 8.08%, $p = .02$).

2.2 Procedure/Intervention

Eligible participants were randomized to study condition and were inducted on medication after being instructed to abstain from opioids for 12–24 hours to present in mild to moderate opioid withdrawal (Clinical Opioid Withdrawal Scale score ≥8) or as deemed appropriate by the study physician. In addition to baseline assessments, biological specimens were collected for testing (urine for drug use testing, blood for HBV, HCV, HIV testing). Participants received a screening test for HCV during approximately the first week in the study. Those who tested positive on screening would have their specimen tested for HCV viral load. Compensation was provided in accordance with local site policies, but typically included compensation for each clinic visit. The University of California Los Angeles Institutional Review Board approved all data collection instruments and procedures.

2.3 Measurements

Baseline assessments included demographics (age, gender, race and ethnicity), number of cigarettes smoked per day, alcohol use (dichotomized into yes/no to register any amount of alcohol consumed), injection drug use, *Risk Behavior Survey* (*RBS*, assesses high risk behaviors of injection drug use and sexual behavior for past 30 days) [24, 25], and *Short Form 36-item Health Survey (SF-36*, a self-report instrument to assess health status over a 4-week-period providing summary scores of physical and mental health components) [25].

Blood specimens were tested for HBV, HCV, and HIV. Initial and confirmatory tests were performed as appropriate. Those who had positive HCV viral load were considered chronically infected. Those with a positive initial screen but negative for current detectable virus were infected but have cleared the virus and developed immunity.

2.4 Statistical Analyses

Group differences among the three HCV groups (1. HCV −/− = both antibody and antigen were negative; 2. HCV +/− = positive antibody and negative antigen; and 3. HCV +/+ = both antibody and antigen were positive) were examined using chi-square tests (for categorical variables) or ANOVA (for continuous variables). For variables with significant differences among the three HCV groups, post-hoc pair-wise comparisons were conducted. Additionally, a multinomial logistic regression model was developed to further examine the multivariate relationship of risk/protective factors with HCV groups. The analysis included demographics; use of tobacco, alcohol and other drugs; injection drug use, high risk sexual behaviors, and other infectious diseases (HIV, HBV) as potential predictors and the HCV groups as the main outcome measure. Odds ratios of the HCV serostatus group (the

reference group is no HCV infection) for the potential covariates were estimated simultaneously.

3. Results

3.1 HCV serostatus

Of the 1,039 participants who completed HCV serological tests, about 34 % exhibited positive results for both HCV antibody and antigen (HCV+/+), indicating a chronic virus infection. Another 14% of participants exhibited a positive result for HCV antibody but a negative result for antigen (HCV+/−), indicating a history of HCV infection but spontaneously cleared virus. Approximately half of the participants (52%) had negative results for presence of both antibody and antigen (HCV−/−), indicating no history of HCV infection.

3.2 Characteristics by HCV serostatus groups

Table 1 summarizes comparisons of baseline characteristics by HCV status. HCV group was not associated with assigned treatment condition. As age increased, so did the risk of HCV positive results; the participants in the HCV+/+ and HCV+/− groups were significantly older than those in the HCV−/− group. Males, in contrast to females, exhibited a higher rate of HCV+/+. Compared to whites, African Americans were more likely to exhibit HCV+/+ and Hispanics were more likely to exhibit HCV+/+ and HCV+/−. HCV status also differed by clinic site location; participants from the west coast clinic sites, compared to those attending east coast sites, exhibited higher prevalences of HCV+/+ and HCV+/−.

Prior substance use history was associated with HCV status. Participants with HCV−/− exhibited lower rates of cigarette smoking, but higher rates of alcohol use, and cannabinoid use than participants with HCV+/− and HCV+/+. However, HCV+/− and HCV+/+ were associated with higher rates of opiate use, cocaine use, and injection drug use in the past 30 days. High risk sexual behavior was not associated with HCV status.

Additionally, HCV status was associated with lowered physical functioning and HBV infection. Participants with HCV+/+, compared to those with HCV−/−, exhibited a lower SF-36 physical component score, specifically in sub-scales of physical functioning and physical role limitation. In contrast to HCV−/−, participants with HCV+/+ and HCV+/− also exhibited a higher prevalence of positive HBV surface antibody. However, HCV status was not significantly associated with HIV infection.

3.3 Multinomial regression model of risk and protection factors by HCV groups

When all risk factors are considered simultaneously in a multivariate analysis, it was found that relative to the HCV−/− group, HCV +/− participants were older, more likely to be Hispanic (relative to white), smoke cigarettes, and be injection drug users. Similarly, HCV +/+ participants were older, Hispanic, and injection drug users. HCV +/+ were also more likely to have used cocaine, but the effect of cigarettes was no longer significant.

4. Discussion

Since first being identified in 1989 [27], HCV has quickly gained attention as a public health concern due to its intense proliferation and negative consequences associated with chronic infection. In comparison with other blood-borne illnesses, HCV is now far more common than HIV/AIDS; and unlike HBV, HCV lacks available vaccines [4]. Because injection drug use is by far the most significant risk factor for contracting HCV, and continued substance use among infected persons raises the risk for developing more serious liver disease [28] and spreading the infection to others, this study sought to better understand the risk factors associated with HCV among patients receiving treatment for opioid dependence.

Study findings show a 48% prevalence of HCV in the opioid dependent sample, a lower rate than the up to 80% estimated of IDUs [2]. This discrepancy in findings is likely influenced by a few key factors: study sample was relatively young, some of the participants were prescription opioid users rather than heroin users and therefore less likely to inject their opioids, individuals with elevated liver function values were screened out due to potential health risks, and participants were enrolled when a brief dip in HCV incidence in the U.S. had occurred [29]. About one third of the sample was HCV +/+, indicating chronic infection. Patients with chronic HCV infection were more likely to report recent injection drug use and use of cocaine. They also tended to be older than those who were HCV −/− or tested positive for only the HCV antibody (HCV +/−). It appears that long-term injection of cocaine among opioid users is particularly risky due to the unsafe injecting practices associated with cocaine (multiple injections during an injection event, increased frequency and quantity) [30, 31]. These findings are in line with the literature showing a higher prevalence rate among long-term IDUs; both older age and severity of substance use are key factors in accelerating HCV disease progression [12, 32].

More controversial in terms of risk is the role of sexual risk behaviors and HCV infection. The literature is not consistent regarding the degree to which HCV transmission is related to unsafe sex practices (i.e., multiple sex partners, unprotected sex). Previous studies show the connection between high risk sex and seropositivity is difficult to tease apart from the relationship between HCV and unsafe drug practices. Specifically, IDUs reporting high risk sexual behaviors with infected partners are often confounded by the tendency also to share injecting paraphernalia with infected partners and to use nonsterile cleaning procedures [10, 33]. This overlap is especially strong among women since they are more likely to use drugs with a male sexual partner [10]. For men, there appear to be independent sexual risk factors. Although not a focus of the current study, the literature indicates that high risk sexual behaviors such as unprotected anal sex, selling sex, and higher number of lifetime sex partners are associated with an increased likelihood of being HCV positive among MSM [10, 34], thereby suggesting that sexual risk and HCV differentially impact various subpopulations of IDUs.

The variability in risk among subpopulations extends to ethnicity. Although previous research of the general population has pointed to increased risk for HCV among African Americans [35], the present study found that Hispanic opioid-dependent participants were at greatest risk for testing positive for HCV and for presenting with chronic HCV. Other

studies examining prevalence rates, spontaneous remission, and chronic HCV have found conflicting results. In a sample of IDUs within the U.S., results indicated that whites and Hispanics were more likely to be HCV positive than blacks [13]. However, Micallef and colleagues [36] found that African Americans are less likely to spontaneously clear HCV, thereby placing them at increased risk for progressing into chronic HCV. Differences in infection rates and disease progression may be indicative of a constellation of risk factors such as access to care, general health behaviors, and stigma/discrimination [37], all of which warrant further investigation in future research.

Some limitations of the current study should be acknowledged. First, lifetime substance use and age of initiation for injection drug use were not included in these analyses. Given that drug injection represents the greatest risk for contracting HCV, knowing the start of injection drug use practices would provide valuable information on when participants were likely to have become infected. Several studies indicate IDUs acquire the virus quickly after injection drug use begins, often taking only one to two years [13, 38]. Having such a time frame would allow for a more accurate picture of risk and disease progression, especially given that HCV can spontaneously disappear in some individuals. More information is needed on which factors elevate risk for progressing into chronic HCV. As discussed above, it appears that racial minorities, Hispanic IDUs in the case of the current study, may be at greater risk depending on length and severity of drug use history.

In line with previous research, our findings show that being older places an individual at greater risk for HCV and chronic HCV [12, 13]. Although not able to address when injection drug use began and infection occurred, the results may indicate that contracting HCV when older makes an individual more likely to move quickly into chronic HCV; conversely, it is possible that older IDUs have been HCV positive for several years and due to long-term use and poor health behaviors, they have not been able to clear the virus. This is a limitation of the study but also of the healthcare system for IDUs. Even among high risk populations, many do not get tested for HCV because testing is too expensive for clinics to do routinely, and by its nature, HCV is generally asymptomatic until serious consequences arise [39].

The relatively little variation in mean scores for physical functioning among the three classes of HCV status may be partially due to HCV's few symptoms prior to severe disease. Although patients with chronic HCV had lowered physical component scores in comparison to HCV negative patients, the small differences in scores may not be clinically significant. Since the current study did not assess other medical conditions, and again does not include a complete history of substance abuse, it is possible limitations in physical functioning may be due to these other factors rather than HCV itself.

On the other hand, the diagnosis of HCV, and to a greater degree chronic HCV, seems to be indicative of a constellation of poorer health and health behaviors. While a vaccine for HBV exists, HCV patients are also more likely to test positive for HBV. More education and health management needs to be interwoven into drug treatment as a means for preventing further disease progression among IDUs and to inhibit the spreading of infection. Addressing this disease, however, is not the current state in healthcare and drug treatment. In a review by Novick and Kreek [40], they found providing HCV medical care to IDUs in

opioid replacement therapy to be feasible and effective; however, the majority of patients do not receive such services. Although side effects from previously used pharmacotherapies and cost of newer medications are notable barriers to widespread use of HCV medication, liver-related mortality can be reduced through practical models focused on regular testing for HIV and HCV, HBV vaccination, and education for disease progression in those HCV +/+ [15]. By increasing prevention and intervention strategies among those at greatest risk, the overall rate of transmission may be substantially slowed.

The current study of an opioid dependent population receiving opioid replacement treatment confirms the high rate of HCV and chronic HCV among drug users. Although the issue of sexual transmission remains debatable, older age, Hispanic ethnicity, and recent substance use appear to be significant risk factors for the disease and disease progression. Future research would benefit from better understanding the role of ethnicity in transmission and/or spontaneous remission. Early intervention and continuous monitoring of IDUs should be the primary focus for addressing this epidemic.

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Table 1

Characteristics by the Three Hepatitis C Groups According to Antibody and Antigen Serostatus

	HCV −/− Antibody (−) Antigen (−) (n=538)	HCV +/− Antibody (+) Antigen (−) (n=147)	HCV +/+ Antibody (+) Antigen (+) (n=354)	Total (n=1,039)
Treatment group, %				
Bup	55.4	47.6	58.8	55.4
Methadone	44.6	52.4	41.2	44.6
Age, % **,12,13				
18–24	23.4	5.4	5.1	14.6
25–34	43.1	21.8	19.2	32.0
35–44	20.8	32.0	25.1	23.9
45–54	11.5	35.4	37.0	23.6
55+	1.1	5.4	13.6	6.0
Mean (SD) **,12,13,23	32.4 (9.2)	41.6 (9.4)	43.4 (10.4)	37.4 (11.1)
Gender, % *,23				
Female	32.3	40.8	28.3	32.1
Male	67.7	59.2	71.8	67.9
Ethnicity, % **,12,13				
White	80.5	69.4	61.3	72.4
Black	6.1	6.8	13.0	8.6
Hispanic	5.6	17.0	18.6	11.7
Others	7.8	6.8	7.1	7.4
Clinic site location, % **,12,13				
West coast	57.1	72.8	78.3	66.5
East coast	42.9	27.2	21.7	33.5
Number of cigarettes smoked per day,% *,12				
0	13.2	3.4	9.3	10.5
<10	25.8	23.1	30.5	27.1
11–20	46.3	53.7	44.1	46.6
21–30	11.7	14.3	11.6	12.0
31+	3.0	5.4	4.5	3.8
Alcohol use, % **,12,13	31.4	21.9	22.9	27.2
Opiate positive, % **,12,13	79.4	93.9	95.5	86.9
Cocaine positive, % **,12,13	29.4	43.5	47.7	37.6
Amphetamine positive, %	7.6	10.2	7.9	8.1
Cannabinoid positive, % **,12,13	26.6	15.7	19.8	22.7
Drug injection in past 30 days, % **12,13	49.4	88.4	88.9	68.4
Multiple sex partners w/o condom, %	7.8	10.2	6.2	7.6
SF-36 Physical component **,13	50.1 (8.8)	49.6 (9.2)	48.0 (9.3)	49.4 (9.2)
SF-36 Mental component	38.5 (12.7)	40.1 (12.2)	40.2 (12.5)	39.1 (12.6)

	HCV −/− Antibody (−) Antigen (−) (n=538)	HCV +/− Antibody (+) Antigen (−) (n=147)	HCV +/+ Antibody (+) Antigen (+) (n=354)	Total (n=1,039)
SF-36 Subscales				
Physical functioning, mean (SD) *,13	50.1 (9.4)	48.9 (9.2)	48.3 (9.4)	49.2 (9.5)
Physical role limitation, mean (SD) *,13	47.6 (11.2)	47.2 (11.5)	45.4 (11.8)	46.7 (11.5)
Bodily pain, mean (SD)	45.2 (11.0)	45.9 (11.7)	44.6 (11.3)	45.2 (11.2)
General health, mean (SD)	45.0 (9.4)	45.5 (9.5)	43.8 (9.8)	44.7 (9.6)
Emotional well-being, mean (SD)	39.4 (11.6)	40.7 (11.2)	40.4 (11.4)	39.6 (11.4)
Emotional role limitation, mean (SD)	42.5 (13.4)	42.4 (13.4)	42.1 (13.6)	42.2 (13.5)
Social functioning, mean (SD)	40.5 (12.1)	42.1 (12.5)	41.8 (11.9)	41.1 (12.1)
Energy/vitality, mean (SD)	44.3 (9.3)	45.9 (8.9)	45.3 (9.3)	44.8 (9.3)
HBV surface antibody (+),% **, 12,13	32.0	46.6	44.9	38.4
Hepatitis B core antibody (+), %	1.1	1.4	1.7	1.4
Hepatitis B affected surface antibody (+), %	11.5	7.5	9.0	10.1
Hepatitis B surface antigen (+), %	0.2	0.7	0.9	0.5
HIV (+), %	0.8	0	1.8	1.0

The chi-square test or ANOVA test:

* $p<0.05$;

** $p<0.01$.

The post-hoc pairwise tests are indicated by superscripts letters, 12, 13, and 23, with (1) HCV −/−, (2) HCV +/−, and (3) HCV +/+; 12 indicates a significant difference ($p<0.05$) between groups HCV−/− and HCV +/−. 13 indicates a significant difference ($p<0.05$) between groups HCV −/− and HCV +/+. 23 indicates a significant difference ($p<0.05$) between groups HCV +/− and HCV +/+.

Table 2

Logistic Regression

	HCV +/− vs. HCV −/−				HCV +/+ vs. HCV −/−			
	ProbChiSq	**OR**	**Lower CL**	**Upper CL**	**ProbChiSq**	**OR**	**Lower CL**	**Upper CL**
Intercept	<.0001				<.0001			
Treatment Group								
Bup	0.5027	0.861	0.557	1.332	0.1276	1.33	0.922	1.92
Age	<.0001**	1.117	1.09	1.144	<.0001**	1.131	1.108	1.155
Gender								
Male	0.068	0.652	0.412	1.032	0.9407	1.015	0.683	1.51
Ethnicity								
Black	0.6657	0.819	0.332	2.023	0.3815	1.368	0.678	2.762
Hispanic	0.0003**	3.912	1.873	8.169	<.0001**	4.589	2.403	8.761
Others	0.7321	1.161	0.494	2.732	0.2793	1.454	0.738	2.866
Clinic site location								
East coast	0.8273	0.946	0.574	1.558	0.3157	0.81	0.537	1.222
# of cigarettes smoked per day	0.0007**	1.513	1.191	1.921	0.0853	1.191	0.976	1.452
Alcohol use	0.2075	0.723	0.437	1.197	0.1168	0.717	0.474	1.087
Opiate positive	0.9089	1.054	0.431	2.579	0.9008	1.046	0.512	2.137
Cocaine positive	0.3454	1.244	0.791	1.957	0.021*	1.557	1.069	2.267
Amphetamine	0.8214	0.915	0.424	1.975	0.4915	0.788	0.399	1.554
Cannabinoid positive	0.4621	0.81	0.462	1.42	0.5252	1.153	0.744	1.786
Drug injection past 30 days	<.0001**	10.728	5.491	20.958	<.0001**	11.413	6.757	19.276
Multiple Sex Partners w/o Condom	0.5688	1.245	0.586	2.644	0.9041	0.959	0.489	1.881
Physical functioning	0.8504	0.997	0.97	1.025	0.9908	1	0.978	1.023
Physical role	0.8403	1.002	0.98	1.025	0.1689	0.987	0.97	1.005
limitation HBV Surface Antibody (+)	0.011**	1.778	1.141	2.771	0.0051**	1.711	1.175	2.491

The chi-square test or ANOVA test:

* p<0.05;

** p<0.01.