Prevalence of Gallbladder Disease among Persons with Hepatitis C Virus Infection in the United States

MPH Capstone Paper

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ABSTRACT

**Background:** Gallstones are a major public health problem and this disorder is one of the most common and costly of all digestive diseases. Although liver cirrhosis is a well-documented risk factor for the formation of gallstones, little is known about the prevalence of gallbladder disease (GBD) in persons with hepatitis C virus (HCV) infection.

**Aims:** To determine the prevalence of GBD in persons with HCV infection in a representative sample of the general adult population of the United States.

**Study Design:** Cross-sectional national survey.


**Participants:** 13,465 persons 20 – 74 years of age for whom data on HCV infection and gallbladder ultrasonography were complete.

**Measurements:** The presence of GBD was ascertained by abdominal ultrasonographic evidence of gallstones or cholecystectomy. The presence of HCV infection was assessed by a positive HCV antibody test and a positive HCV RNA test.

**Results:** Of the 13,465 persons evaluated, 1.6% (95% CI, 1.1% – 2.1%) had chronic HCV infection and 12.5% (95% CI, 11.3% – 13.7%) had GBD. After adjusting for potential confounding variables, the relative odds of gallstones (OR = 3.20; 95% CI 1.08 – 9.45; p = 0.036), cholecystectomy (OR = 4.57; 95% CI 1.57 – 13.27; p = 0.006), and GBD (OR = 3.86; 95% CI, 1.51 – 9.86; p = 0.006) among HCV positive men was significantly elevated compared to HCV negative men. In contrast, the adjusted relative odds of gallstones (OR = 2.55; 95% CI, 0.58 – 11.25; p = 0.211), cholecystectomy (OR = 0.70; 95% CI, 0.21 – 2.37; p = 0.563), and GBD (OR = 1.59; 95% CI, (0.54 – 4.64; p = 0.391) among HCV positive women was not significantly higher compared with HCV negative women. The prevalence of GBD differed significantly according to HCV genotype (p = 0.028), with the prevalence of GBD being highest in persons infected with genotype 2a and lowest in those with genotype 4. The relative odds of GBD increased significantly with the severity of liver disease as assessed by elevated serum total bilirubin levels and low levels of serum albumin and platelet counts.

**Conclusions:** In the United States, HCV infection is a major risk factor for GBD among men but not in women and GBD was more common in those with severe liver disease.
Gallstones are a major public health problem and this disorder is one of the most common and costly of all digestive diseases (1). The Third National Health and Nutrition Examination Survey (NHANES III) estimated that 20.5 million persons in the United States had gallbladder disease (GBD) (2). There are more than one thousand deaths per year from GBD in the United States, and the mortality rate is 0.84 per 100,000 persons (1). Furthermore, the annual direct and indirect costs of GBD in the United States in the year 2000 was approximately 6.5 billion dollars, and it is the second most costly digestive disease (1).

Although liver cirrhosis is a well-documented risk factor for the formation of gallstones (3-21), little is known about the prevalence of GBD in persons with hepatitis C virus (HCV) infection. In addition to GBD, HCV infection is also an important public health problem in the United States and it is a leading cause of chronic liver disease and cirrhosis (22, 23). Data from NHANES III estimated that approximately 3.9 million people (1.8% of the population) have been infected with HCV in the United States, and approximately 2.7 million people have chronic infection (24). Despite the high prevalence of both GBD and HCV infection in the United States, no population-based studies of GBD have been conducted among persons with HCV infection.

Ultrasonography of the gallbladder and HCV testing were both performed as part of NHANES III, resulting in population-based estimates derived from approximately 14,000 participants (25). The primary aim of this study was to determine the prevalence of GBD in persons with HCV infection in the United States. We hypothesized that persons with HCV infection have a higher prevalence of GBD than those without HCV infection after adjusting for important confounding variables.

**METHODS**

**Study Population**

NHANES III was conducted from 1988 – 1994 by the National Center for Health Statistics to obtain national statistics on the health and nutritional status of the noninstitutionalized civilian population of the United States by means of household interviews, as well as standardized physical examinations,
abdominal ultrasonography, and collection of blood samples in special mobile examination centers. NHANES III included a sample of 33,994 persons at least two months of age at 89 randomly selected locations throughout the United States (25). The study protocol was reviewed and approved by an institutional review board at the Centers for Disease Control and Prevention and all participants provided written informed consent.

NHANES III was based on a complex, stratified, multistage, probability-sample design (25). Persons less than 5 years of age or 60 years of age or older, non-Hispanic blacks, and Mexican Americans were sampled at higher frequencies than other persons. After weighting on the basis of age, sex, race/ethnicity, and level of education, the distribution of participants was similar to that of the United States population as a whole.

The target population for the gallbladder examination in NHANES III was the household population of adults 20 – 74 years of age. A total of 16,115 persons 20 – 74 years of age were interviewed at home, and 14,294 of these individuals completed the ultrasound examination of the gallbladder in the mobile examination centers. We excluded 56 persons because of inability to properly visualize the gallbladder lumen (9 with porcelain gallbladder and 47 because the gallbladder was not well seen), leaving 14,238 with complete ultrasound examinations. Among these 14,238 persons, 13,495 individuals had HCV antibody testing performed. After excluding 30 individuals with indeterminate HCV antibody test results, the remaining 13,465 persons constitute the study sample (Figure 1).

**Study Design**

Ultrasound examinations were conducted with persons in both supine and left decubitus positions with a Toshiba (Tustin, CA) SSA-90A machine using 3.75-MHz and 5.0-MHz transducers (25). A diagnosis of gallstones required 2 views showing echoes within the gallbladder and echo shadowing. If a right upper quadrant or epigastric scar was observed and the gallbladder was not seen, it was concluded that a cholecystectomy had been performed.

All examinations were videotaped for an independent review by expert radiologists without knowledge of the technician's diagnosis. When the diagnosis made by the ultrasonographer and
radiologist differed, the videotape was reviewed by a senior radiologist for final adjudication. Agreement between examining ultrasonographers and videotape review by radiologists was 99% with a kappa statistic of 0.94 for the diagnosis of GBD (2).

Presence of antibody to HCV was assessed by using a second-generation enzyme immunoassay test (Abbott Laboratories, Chicago, Illinois). Positive specimens were tested in duplicate, and repeatedly positive samples were tested again by using the HCV MATRIX assay (Abbott Laboratories). Specimens that were positive according to the HCV MATRIX assay were considered to be HCV antibody positive (24).

Testing for HCV RNA using reverse-transcriptase polymerase-chain-reaction amplification of the 5' noncoding region was performed on HCV antibody positive samples (24). Samples found to be negative for HCV RNA were extracted a second time by the same procedure with an additional incubation at 50 degrees Celsius for 45 minutes with 25 units of reverse transcriptase (Boehringer Mannheim Diagnostics, Indianapolis, IN) and 10 units of RNAsin (Boehringer Mannheim Diagnostics). The genotype of HCV RNA positive samples were determined by sequencing of 300 nucleotides in the NS5b region (24). Tests for hepatitis B surface antigen were performed using a sandwich radioimmunoassay (Abbott Laboratories).

In addition to abdominal ultrasonography and HCV testing, NHANES III collected information on many other variables that could potentially confound the relationship between HCV infection and GBD (2). For both men and women, potential covariates that were considered in these analyses included age, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, and other), body mass index (weight in kilograms divided by the square of height in meters), waist to hip circumference ratio, highest completed year of education, poverty income ratio, breakfast frequency (everyday, some days, rarely, weekends only, or never), voluntary weight loss in the prior 12 months, monthly leisure physical activity as measured by the self-reported frequencies of 9 activities (walking, running or jogging, dancing, swimming, bicycling, gardening, lifting weights, calisthenics, and aerobics), serum total cholesterol levels, presence of diabetes (determined by self-report of a physician diagnosis of diabetes), alcohol use
(never drinker, past drinker, less than 1 drink per day, 1 – 2 drinks per day, and more than 2 drinks per day), and tobacco use (never smoker, past smoker, less than 1 pack per day, and at least 1 pack per day). In addition to the potential confounding variables listed above, covariates that were included in the analyses for women included the number of live births and duration of oral contraceptive use in months.

**Study Outcomes**

The primary outcome of this study was the prevalence and relative odds of GBD among HCV positive persons compared to those without HCV infection. For the analysis of HCV status, persons were considered HCV positive if they had a positive HCV antibody and were HCV RNA positive by polymerase-chain-reaction. Persons were considered HCV negative if they were HCV antibody negative or if they were HCV antibody positive but HCV RNA was not detected by polymerase-chain-reaction. GBD was defined by the presence of one or more gallstones on ultrasound examination or if there was evidence of surgical removal of the gallbladder.

Secondary outcomes of this study were the prevalence of GBD in HCV positive persons according to the genotype of HCV infection, determination of the relative odds of GBD in HCV positive persons according to the severity of liver disease, and the prevalence of GBD among hepatitis B virus (HBV) positive subjects. The severity of liver disease was determined by serum total bilirubin levels, serum albumin levels, platelet counts, and the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio. Patients were considered HBV positive if they had hepatitis B surface antigen detected in serum.

**Statistical Analysis**

General descriptive analysis was performed to compare participants with and those without HCV infection. Using statistical techniques to account for the complex survey design of NHANES III, categorical variables were compared using Pearson chi-square tests, while continuous variables were compared using t-tests.

Because of sex differences in the prevalence of and risk factors for HCV infection and GBD in the United States, we conducted separate analyses for men and women (2). Univariate and multivariate
complex survey logistic regression techniques were used to determine the sex-specific crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) of GBD with respect to HCV and HBV infection. All statistical analyses were performed using Stata SE software, version 8.2 (Stata Corp., College Station, TX). Sampling weights based on United States Census data describing age, sex, ethnicity, income, and geographic location of the United States population were used in all analyses to provide accurate estimates that were representative of the United States population during that time. These sampling weights account for the unequal probabilities of selection as a result of the cluster design, non-response, and the planned oversampling of certain ethnic minority populations (25).

RESULTS

Participant Characteristics

Antibodies to HCV were present in 2.3% (95% CI, 1.8% – 2.8%) of the 13,465 participants. The prevalence of antibodies to HCV was 3.1% (95% CI, 2.3% – 4.0%) in men and 1.5% (95% CI, 1.1% – 1.9%) in women, and this difference was statistically significant (p = 0.001).

Among HCV antibody positive persons, 76.6% (95% CI, 66.9% – 84.2%) were HCV RNA positive by polymerase-chain-reaction and, therefore, had chronic HCV infection with viremia. Overall, 1.6% (95% CI, 1.1% – 2.1%) of the population was HCV RNA positive, and the prevalence was significantly higher in men (2.2%; 95% CI, 1.4% – 3.0%) than in women (1.0%; 95%, CI 0.6% – 1.5%; p = 0.004).

The population characteristics stratified by HCV status are shown in Table 1. Compared to HCV negative persons, participants who were HCV positive were significantly younger, were more likely to be men, were less likely to be white, had a lower education and poverty income ratio, were less likely to voluntarily try to lose weight in the past 12 months, had lower serum total cholesterol levels, consumed more alcohol, and were more likely to smoke.

Overall Prevalence of GBD
The prevalence of GBD in the 13,465 persons in this study was 12.5% (95% CI, 11.3% – 13.7%), including gallstones in 7.1% (95% CI, 6.3% – 7.9%) and cholecystectomy in 5.4% (95% CI, 4.8% – 5.9%). The overall prevalence of gallstones (8.6% [95% CI, 7.4% – 9.8%] vs. 5.6% [95% CI, 4.7% – 6.5%], p < 0.001), prior cholecystectomy (8.1% [95% CI, 7.2% – 9.0%] vs. 2.4% [95% CI, 1.8% – 3.1%], p < 0.001), and GBD (16.7% [95% CI, 15.1% – 18.4%] vs. 8.0% [95% CI, 6.7% – 9.3%], p < 0.001) were all significantly higher in women than in men.

**GBD in HCV Positive Persons**

Overall, there were approximately 404,847 (95% CI, 135,550 – 674,144) persons with chronic HCV infection and GBD in the United States. The crude prevalence of gallstones, cholecystectomy, and GBD (gallstones and cholecystectomy combined) among HCV positive persons is shown in Table 2. For both men and women, the crude prevalence of GBD was higher in HCV positive persons than in those who were HCV negative, although only the crude relative odds of gallstones in women was statistically significant (OR = 2.84; 95% CI, 1.07 – 7.51; p = 0.036).

The prevalence of GBD increased with age among men with HCV and among men without HCV (Figure 2A). The proportion of men with GBD was higher in HCV positive persons than in HCV negative persons for all age groups except those 20 – 29 years of age. Among HCV positive women, the highest prevalence of GBD was seen among those persons 50 – 59 years of age, while the prevalence of GBD increased in a linear fashion with age among HCV negative women (Figure 2B). The proportion with GBD was higher in HCV positive women than in HCV negative women for all age groups except those 20 – 29 years of age.

The prevalence of GBD was higher in HCV positive men compared with HCV negative men among non-Hispanic blacks and Mexican Americans (Figure 3A). In contrast, the prevalence of GBD was similar in HCV positive and HCV negative non-Hispanic white men. The prevalence of GBD was higher in HCV positive women compared with HCV negative women for non-Hispanic whites, non-Hispanic blacks, and Mexican Americans (Figure 3B).
Potential risk factors that might confound the relationship between HCV and GBD were evaluated in sex-specific multivariate logistic regression models (Table 2). After adjusting for potential confounding variables, the relative odds of gallstones (OR = 3.20; 95% CI 1.08 – 9.45; p = 0.036), cholecystectomy (OR = 4.57; 95% CI 1.57 – 13.27; p = 0.006), and GBD (OR = 3.86; 95% CI, 1.51 – 9.86; p = 0.006) among HCV positive men was significantly elevated compared to HCV negative men. In contrast, the adjusted relative odds of gallstones, cholecystectomy, and GBD among HCV positive women was not significantly higher compared to HCV negative women.

Prevalence of GBD According to HCV Genotype

Genotype was determined for 96.9% of the HCV positive samples and 56.2% were classified as 1a, 14.4% as 1b, 2.9% as 2a, 11.0% as 2b, 8.2% as 3a, 0.9% as 4, and 6.4% as genotype 6. The prevalence of GBD stratified by HCV genotype is shown in Figure 4. The proportion of persons that had GBD differed significantly according to genotype (p = 0.028), with the prevalence of GBD being highest in persons infected with genotype 2a and lowest in those with genotype 4. However, there was no statistically significant difference in the prevalence of GBD among persons with genotype 1 (17.1%; 95% CI, 4.4% – 29.9%) compared to those with other genotypes (15.8%; 95% CI, 0.0% – 34.8%; p = 0.911).

GBD and the Severity of Liver Disease in HCV Positive Persons

In order to determine whether more severe liver disease was associated with a higher prevalence of GBD among HCV infected persons, we evaluated the association between GBD and serum total bilirubin levels, serum albumin levels, platelet counts, and the AST/ALT ratio (Table 3). The relative odds of GBD increased with increasing levels of serum total bilirubin levels and this association remained statistically significant after adjusting for age, gender, and race/ethnicity. In addition, lower serum albumin levels and lower platelet counts were associated with an increased relative odds of GBD in both unadjusted and adjusted multivariate logistic regression models. Although an AST/ALT ratio of > 1.00 was significantly associated with an increased relative odds of GBD in the unadjusted analysis, the association did not persist after adjusting for age, sex, and race/ethnicity.

GBD in Hepatitis B Virus-Infected Persons
The prevalence of HBV infection among the study population was 0.45% (95% CI, 0.29% – 0.60%). The proportion of men with HBV infection (0.60%, 95% CI, 0.34% – 0.85%) was significantly higher than the proportion of women infected with HBV (0.30%; 95% CI, 0.15% – 0.46%; p = 0.033). There was no increase in the prevalence of GBD among men (OR = 0.26; 95% CI, 0.05 – 1.25; p = 0.092) or women (OR = 0.47; 95% CI, 0.06 – 3.42; p = 0.445) with HBV infection compared to those without HBV infection even after adjusting for all potential confounding variables.

DISCUSSION

Ultrasonography is a rapid, non-invasive method of imaging the gallbladder, and this technique has contributed greatly to our understanding of the epidemiology of and risk factors for GBD (26). The risk of GBD increases with age (26, 27), and the prevalence is as high as 25.3% in men and 33.1% in women 60 – 74 years of age in the United States (2). Overall, the prevalence of GBD in the United States is higher in women (16.6%) than in men (7.9%) between the ages of 20 – 74 years (2). Population-based studies have revealed a marked variation in the prevalence of GBD among different racial/ethnic groups (2, 28, 29). The age-standardized prevalence of GBD in the United States was similar for non-Hispanic white men (8.6%) and Mexican American men (8.9%), and both were higher than in non-Hispanic black men (5.3%). Among women, the age-adjusted prevalence was higher in Mexican Americans (26.7%) than in non-Hispanic whites (16.6%) and non-Hispanic blacks (13.9%) (2), and American Indian and Hispanic women are at particularly high-risk of developing GBD (28, 29).

In addition to age, sex, and race/ethnicity, other potential risk factors for GBD include obesity (2, 30-32), rapid weight loss (31), lower levels of physical activity (2, 33, 34), pregnancy (35-37), increasing number of live births (2), oral contraceptive use and estrogen replacement therapy (38, 39), diabetes mellitus (2, 40-42), abstinence from alcohol (2, 41, 43), smoking (2), low total serum cholesterol levels (2, 15), low levels of coffee consumption (44, 45), and genetic factors (46, 47). However, some of these variables have been inconsistently found to be associated with GBD and these risk factors may differ considerably among men and women (2, 15).
Liver cirrhosis has also been shown to be an important risk factor for the development of GBD (3-21). Although cholesterol stones are the most common type of gallstones in the general population, pigment stones are the most prevalent type in cirrhotic patients (3, 6, 48). Several investigators have noted that the risk of GBD varies according to the etiology of cirrhosis (9, 20). In a prospective study of 165 cirrhotic patients followed for a mean of 33 months, the incidence of new gallstones was 28.9% in alcoholic cirrhosis but only 1.9% in those with cirrhosis from viral hepatitis (9). In contrast, Buchner and Sonnenberg (20) found that the prevalence of gallstones was lower in patients with alcoholic cirrhosis (9%) compared to those with non-alcoholic cirrhosis (14%).

In contrast to the abundance of literature on the association between cirrhosis and GBD, we are unaware of any other population-based studies of the relationship between HCV infection and GBD. In a retrospective review of 1,028 subjects undergoing a periodic health examination at China Medical College Hospital in Taiwan, multivariate analysis identified HCV infection as a risk factor for GBD in women (OR = 3.6; 95% CI, 1.4 – 9.7) but not in men (49). In contrast, O’Sullivan et al. (50) found that the incidence of gallstones in patients infected with HCV was no different than the incidence of gallstones in the general population in Ireland.

In the present study, we found that HCV infection was a strong risk factor for GBD in men (OR = 3.86; 95% CI, 1.51 – 9.86) but not in women (OR = 1.59; 95% CI, 0.54 – 4.64). The reason for the sex-specific differences in the association between HCV infection and GBD are not known. However, these findings are in agreement with other studies that have shown that cirrhosis is a risk factor for GBD in men but not in women (5, 18). It is likely that the pathophysiology of and risk factors for gallstone formation differ among men and women (2, 15). Alternatively, we may have failed to detect a statistically significant association between HCV infection and GBD due to the small proportion of women with chronic HCV (1.0%) or due to the fact that women already have a high prevalence of GBD even in the absence of HCV infection.

The mechanisms leading to the development of gallstones in patients with cirrhosis of the liver are not well understood. The increased risk of gallstone formation in cirrhotic patients, especially in those
with advanced liver disease, is likely multifactorial and proposed mechanisms include reduced hepatic synthesis and transport of bile salts (51), impaired gallbladder motility (19, 52, 53), high estrogen levels (17, 54), and chronic hemolysis secondary to hypersplenism (4, 6). Impaired gallbladder motility can result in decreased gallbladder emptying in response to a meal, bile stasis, and increased gallstone formation, and one study proposed that impaired gallbladder motility in cirrhotics with gallstones is due to autonomic dysfunction (53). Although high estrogen levels have been suggested as a possible mechanism of increased gallstone formation in cirrhotic patients, Li et al. (19) did not find any significant differences in plasma levels of sex hormones (estradiol and testosterone) between cirrhotic patients with and those without gallstones.

In addition to the potential mechanisms of increased gallstone formation in cirrhotic patients described above, direct infection of the gallbladder by HCV may also play an important role in the development of GBD. Loriot et al. (55) demonstrated that HCV can successfully infect gallbladder epithelial cells. Although HCV replication in gallbladder epithelial cells was low, the results were highly reproducible in that study. Other investigators have also detected HCV RNA and HCV antigens in gallbladder specimens obtained from HCV-infected patients at the time of autopsy (56). It is possible that HCV infection of the gallbladder may increase the risk of gallstone formation by causing altered gallbladder mucosal function or gallbladder dyssmotility, and further investigations to address this interesting hypothesis are needed.

The present investigation found that the relative odds of GBD among persons with HCV infection increased with the severity of liver disease as assessed by serum total bilirubin levels, serum albumin levels, and platelet counts. Several other studies have also demonstrated that the prevalence and incidence of GBD was significantly higher in patients with advanced cirrhosis compared to those with well-compensated liver disease (4-6, 8-11, 13, 18, 19). In a prospective study of 165 cirrhotic patients, Fornari et al. (9) noted that the cumulative incidence of gallstones at 48 months was 49.3% in patients with Child-Pugh class C cirrhosis compared with 24.0% in patients with class B and 6.4% in those with class A cirrhosis.
The risk of gallstones becoming symptomatic is higher in patients with cirrhosis due to viral hepatitis than in those with alcoholic cirrhosis (21). In addition, patients with cirrhosis are more likely to undergo cholecystectomy for emergent reasons than those without liver disease (57). These findings, as well as the results of the present study showing a high prevalence of GBD in persons with advanced liver disease in the United States, have important implications because cholecystectomy for symptomatic gallstones in patients with advanced liver disease is associated with a high risk of morbidity and mortality (57, 58).

After adjusting for potential confounding variables, the present study did not find a statistically significant association between HBV infection and GBD. It is interesting to note that the adjusted relative odds of GBD in HBV-infected men (OR = 0.26; 95% CI, 0.05 – 1.25) and women (OR = 0.47; 95% CI, 0.06 – 3.42) in the NHANES III study participants was less than 1, suggesting a protective effect of HBV on the development of GBD. Although some investigators have shown that HBV was not a risk factor for GBD (59-61), others reported that HBV infection was a strong risk factor for GBD (62). Interestingly, one study of 603 patients with chronic hepatitis or cirrhosis found that gallstones were present in only 11.9% of HBV-infected patients compared with 36.2% of those without HBV, and also demonstrated that HBV infection was protective for the development of gallstones in multivariate analysis (13).

The main strength of using the NHANES III data is that it included a large sample size and it allowed for the determination of direct estimates of the prevalence of GBD among HCV-infected persons in the United States population rather than relying on the prevalence in a highly selected population. Other strengths of NHANES III included the collection of detailed data on risk factors for GBD, the use of ultrasonography to make the diagnosis of GBD, and the availability of HCV RNA testing to diagnose chronic HCV infection.

However, several limitations should be considered when interpreting our findings. Due to the cross-sectional design of NHANES III, a temporal relationship between HCV infection and GBD could not be established. In addition, some risk factors for GBD may have changed from the time when gallstones formed and data were not available on some potential risk factors such as rapid weight loss.
Another potential limitation is that cholesterol and pigment stones were not differentiated in this study, and, therefore, we cannot be sure that the observed differences between HCV positive and HCV negative persons were due to differences in the risk of a particular type of gallstone. Finally, another limitation of this study is the use of surrogate markers (serum total bilirubin, albumin, platelet count, and AST/ALT ratio) to determine the severity of liver disease since liver biopsies were not performed.

In conclusion, our study demonstrates that chronic HCV infection is an important risk factor for GBD in men but not in women in the United States. Among persons with HCV infection, the prevalence of GBD is highest among those with more severe liver disease. The findings of this study are important because of the large number of persons in the United States with HCV infection and GBD. In addition, this study has important public health implications because cholecystectomy for symptomatic gallstones in patients with advanced liver disease is associated with a high risk of morbidity and mortality. Further research is needed to determine the temporal relationship between HCV infection and GBD, as well as the incidence of symptomatic gallstones, the optimal management of GBD, and the outcomes of cholecystectomy among persons with HCV. In addition, future studies to evaluate the impact of antiviral therapy on the incidence of GBD among persons with HCV infection in the United States are warranted.
REFERENCES


Table 1. Characteristics of the 13,465 Participants Stratified by HCV Status*

<table>
<thead>
<tr>
<th></th>
<th>HCV Positive</th>
<th>HCV Negative</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>39.1 ± 0.99</td>
<td>42.4 ± 0.36</td>
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<tr>
<td>Men</td>
<td>66.7%</td>
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<td>Women</td>
<td>33.3%</td>
<td>51.7%</td>
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<td>Non-Hispanic white</td>
<td>58.3%</td>
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<td>Non-Hispanic black</td>
<td>22.2%</td>
<td>10.4%</td>
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<tr>
<td>Mexican American</td>
<td>6.9%</td>
<td>5.3%</td>
<td></td>
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<tr>
<td>Other</td>
<td>12.6%</td>
<td>7.8%</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>25.7 ± 0.55</td>
<td>26.6 ± 0.12</td>
<td>0.096</td>
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<td>Waist to hip ratio</td>
<td>0.92 ± 0.007</td>
<td>0.91 ± 0.002</td>
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<td>Highest year of education completed</td>
<td>11.1 ± 0.25</td>
<td>12.5 ± 0.09</td>
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<td>Poverty income ratio†</td>
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<td>3.1 ± 0.06</td>
<td>&lt; 0.001</td>
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<td>Breakfast frequency</td>
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<td>Some days</td>
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<tr>
<td>Rarely</td>
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<td>Weekends</td>
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<td>Never</td>
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<td>Voluntary weight loss in last 12 months</td>
<td>24.3%</td>
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<td>Number of leisure physical activities in last month</td>
<td>23.2 ± 4.3</td>
<td>21.2 ± 0.59</td>
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<td>Serum total cholesterol level (mg/dL)</td>
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<td>203.6 ± 0.81</td>
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<td>4.9%</td>
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<tr>
<td>Alcohol use</td>
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<td>Never drinker</td>
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<td>12.1%</td>
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<td>Past drinker</td>
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<td>Less than 1 drink per day</td>
<td>23.8%</td>
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<tr>
<td>1 – 2 drinks per day</td>
<td>19.7%</td>
<td>8.8%</td>
<td></td>
</tr>
<tr>
<td>More than 2 drinks per day</td>
<td>26.3%</td>
<td>6.4%</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Never smoker</td>
<td>19.1%</td>
<td>45.5%</td>
<td></td>
</tr>
<tr>
<td>Past smoker</td>
<td>16.8%</td>
<td>25.6%</td>
<td></td>
</tr>
<tr>
<td>Less than 1 pack per day</td>
<td>24.8%</td>
<td>12.6%</td>
<td></td>
</tr>
<tr>
<td>1 or more packs per day</td>
<td>39.3%</td>
<td>16.4%</td>
<td></td>
</tr>
<tr>
<td>Number of live births‡</td>
<td>2.5 ± 0.23</td>
<td>2.5 ± 0.04</td>
<td>0.810</td>
</tr>
<tr>
<td>Duration of oral contraceptive use in months‡</td>
<td>30.8 ± 6.8</td>
<td>35.3 ± 1.3</td>
<td>0.504</td>
</tr>
</tbody>
</table>

*Continuous variables are expressed as mean ± standard error. Categorical variables are expressed as percentages; actual numbers are not shown because the percentages incorporate sampling weights to account for the complex survey design.

†The poverty income ratio was based on self-report of family income, family size, and tables published annually by the U.S. Census Bureau. A poverty income ratio below 1.0 indicates that the person was below the poverty level.

‡Estimates are for women only.
Table 2. Relative Odds of Gallbladder Disease among HCV Positive Persons Compared to HCV Negative Persons

<table>
<thead>
<tr>
<th></th>
<th>Crude Prevalence (95% CI)</th>
<th>Odds Ratios (95% CI)*</th>
<th>Crude</th>
<th>Fully Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV Positive</td>
<td>HCV Negative</td>
<td>Crude</td>
<td>Fully Adjusted</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallstones</td>
<td>7.5% (0.0% – 15.1%)</td>
<td>5.5% (4.6% – 6.4%)</td>
<td>1.40 (0.46 – 4.29)</td>
<td>3.20 (1.08 – 9.45)</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>3.0% (0.0% – 7.3%)</td>
<td>2.4% (1.8% – 3.1%)</td>
<td>1.23 (0.30 – 5.11)</td>
<td>4.57 (1.57 – 13.27)</td>
</tr>
<tr>
<td>Gallbladder Disease‡</td>
<td>10.5% (0.4% – 20.7%)</td>
<td>7.9% (6.7% – 9.2%)</td>
<td>1.36 (0.47 – 3.97)</td>
<td>3.86 (1.51 – 9.86)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallstones</td>
<td>20.8% (5.0% – 36.5%)</td>
<td>8.5% (7.2% – 9.7%)</td>
<td>2.84 (1.07 – 7.51)</td>
<td>2.55 (0.58 – 11.25)</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>7.1% (1.2% – 13.0%)</td>
<td>8.1% (7.2% - 9.0%)</td>
<td>0.86 (0.35 – 2.12)</td>
<td>0.70 (0.21 – 2.37)</td>
</tr>
<tr>
<td>Gallbladder Disease‡</td>
<td>27.9% (13.6% – 42.1%)</td>
<td>16.6% (15.0% – 18.3%)</td>
<td>1.94 (0.94 – 4.01)</td>
<td>1.59 (0.54 – 4.64)</td>
</tr>
</tbody>
</table>

*Odds ratios are for the comparison of HCV positive persons to those that were HCV negative.

†For both men and women, fully adjusted odds ratios were adjusted for age, race/ethnicity, body mass index, waist to hip circumference ratio, highest completed year of education, poverty income ratio, breakfast frequency, voluntary weight loss in the prior 12 months, monthly leisure physical activity, serum total cholesterol, presence of diabetes, alcohol use, and tobacco use. In addition, the fully adjusted odds ratios for women were also adjusted for the number of live births and duration of oral contraceptive use.

‡Gallbladder disease is defined as the presence of gallstones or evidence of cholecystectomy.
Table 3. Relative Odds of Gallbladder Disease among HCV Positive Persons According to the Severity of Liver Disease*

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-Value</td>
</tr>
<tr>
<td>Serum total bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1.0 mg/dL</td>
<td>1.00 (reference)</td>
<td>--</td>
</tr>
<tr>
<td>1.1 – 2.0 mg/dL</td>
<td>1.32 (0.39 – 4.50)</td>
<td>0.652</td>
</tr>
<tr>
<td>&gt; 2.0 mg/dL</td>
<td>39.79 (7.50 – 211.14)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum albumin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3.4 g/dL</td>
<td>1.00 (reference)</td>
<td>--</td>
</tr>
<tr>
<td>3.1 – 3.4 g/dL</td>
<td>26.85 (6.90 – 104.49)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≤ 3.0 g/dL</td>
<td>17.88 (3.12 – 102.30)</td>
<td>0.002</td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 200 x 10^9/µL</td>
<td>1.00 (reference)</td>
<td>--</td>
</tr>
<tr>
<td>100 – 199 x 10^9/µL</td>
<td>3.28 (0.76 – 14.23)</td>
<td>0.110</td>
</tr>
<tr>
<td>&lt; 100 x 10^9/µL</td>
<td>42.74 (7.62 – 239.62)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1.00</td>
<td>1.00 (reference)</td>
<td>--</td>
</tr>
<tr>
<td>&gt; 1.00</td>
<td>3.69 (1.10 – 12.44)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

*The severity of liver disease was assessed by serum levels of total bilirubin (reference range, ≤ 1.0 mg/dL), serum albumin (reference range, 3.4 – 5.0 g/dL), platelet counts (reference range, 200 – 400 x 10^9/µL), and the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio.

† Adjusted for age, sex, and race/ethnicity.
Figure 1. Determination of the Study Sample

- 33,994 Persons Interviewed
- 16,115 20 – 74 Years of Age
- 14,294 Ultrasonography Performed
- 14,238 Valid Ultrasound Exam
- 13,495 HCV Testing Performed
- 13,465 Final Study Sample
Figure 2A. Prevalence of Gallbladder Disease among HCV Positive and HCV Negative Men Stratified by Age

Figure 2B. Prevalence of Gallbladder Disease among HCV Positive and HCV Negative Women Stratified by Age
Figure 3A. Prevalence of Gallbladder Disease among HCV Positive and HCV Negative Men Stratified by Race/Ethnicity

![Bar chart showing prevalence of gallbladder disease among HCV positive and HCV negative men stratified by race/ethnicity.]

Figure 3B. Prevalence of Gallbladder Disease among HCV Positive and HCV Negative Women Stratified by Race/Ethnicity

![Bar chart showing prevalence of gallbladder disease among HCV positive and HCV negative women stratified by race/ethnicity.]
Figure 4. Prevalence of Gallbladder Disease Stratified by HCV Genotype

p = 0.028 by Pearson chi-square analysis