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Association of hepatitis C infection and acute coronary syndrome

A case-control study

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Abstract

Infections with hepatitis C virus (HCV) represent a substantial national and international public health burden. HCV has been associated with numerous extrahepatic conditions and can lead to metabolic derangements that are associated with atherosclerosis and cardiovascular disease. We investigated whether HCV infection is associated with an increased number of acute coronary syndrome (ACS) events among hospitalized patients in an inner-city tertiary hospital.

We performed a matched (age, sex, and race/ethnicity) case-control study on patients at least 18 years old admitted to inpatient medical and cardiac services at the University of Maryland Medical Center from 2015 through 2018. The primary outcome was ACS and the primary exposure was HCV infection. Covariates of interest included: alcohol use, tobacco use, illicit drug use, hypertension, diabetes mellitus, human immunodeficiency virus infection, body mass index, dyslipidemia, and family history of coronary heart disease. Covariates with significant associations with both exposure and outcome in bivariate analyses were included in the multivariable analyses of the final adjusted model.

There were 1555 cases and 3110 controls included in the final sample. Almost 2% of cases and 2.4% of controls were HCV infected. In adjusted models, there was no significant association found between experiencing an ACS event in those with HCV infection compared to those without HCV infection (odds ratio 0.71, 95% confidence interval 0.45–1.11).

We found no significant association between HCV infection and ACS in our study population. However, given the mixed existing literature, the association between HCV and ACS warrants further investigation in future prospective cohort and/or interventional studies.

Abbreviations: ACS = acute coronary syndrome, AMI = acute myocardial infarction, BMI = body mass index, CHD = coronary heart disease, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IHD = ischemic heart disease, MI = myocardial infarction, NHANES = National Health and Nutrition Examination Surveys, OR = odds ratio, RNA = ribonucleic acid, UMMC = University of Maryland Medical Center.

Keywords: acute coronary syndrome, atherosclerosis, cardiovascular disease, coronary heart disease, hepatitis C

1. Introduction

Infections with hepatitis C virus (HCV) represent a national and international public health burden, with 180 million people infected worldwide and 4.1 million in the United States alone.[1] Infection with HCV is the leading indication for liver transplant and approaches alcoholic liver disease as a leading cause of liver-related death in the United States. The World Health Organization projects that ischemic heart disease (IHD) will be among the

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top three causes of global mortality and disability by 2030,[2] and data suggests that there may be an association between HCV infection and atherosclerotic disease.[3] If such an association exists, the intersection of these epidemics could present significant challenges among clinicians and public health officials in reducing morbidity and mortality among high-risk patient populations.

HCV has been associated with numerous extrahepatic conditions, and many of its long-term liver sequelae can lead to metabolic derangements associated with atherosclerosis.[4] As such, there is biological plausibility for the association between chronic HCV infection and atherosclerosis. A large retrospective cohort study from the University of Arkansas for Medical Sciences found that HCV seropositivity was an independent risk factor for incident coronary heart disease (CHD) events, even after adjustments for age, gender, hypertension, diabetes, and chronic obstructive pulmonary disease.[5] In contrast, another retrospective cohort study from the National Health and Nutrition Examination Surveys (NHANES) found that chronic HCV infection was independently associated with congestive heart failure but not IHD or stroke.[6] Conflicting results in the literature represent an inconclusive relationship between HCV infection and IHD that requires further investigation.[3–8] Furthermore, a majority of study populations in the literature include a high proportion of Caucasian males while high-risk minority groups, who are disproportionately affected, are underrepresented. African Americans account for approximately 20% of the population infected with HCV but represent approximately 13% of the United States population.[9] In the Third National Health and Nutrition Examination Survey (NHANES III) from 1988–1994, African Americans had greater than two times the seroprevalence of HCV compared with non-Hispanic whites. A subsequent NHANES study in 1999–2002 found that this racial difference persisted, with prevalence of hepatitis C in non-Hispanic blacks being double that of non-Hispanic whites.[9]

Therefore, we investigated whether HCV infection was associated with increased hospital admissions for acute coronary syndrome (ACS) events among hospitalized patients in an inner-city tertiary hospital. We hypothesized that HCV infection will be associated with hospital admissions for ACS events compared to hospital admissions for other conditions. Elucidating the relationship between HCV infection and IHD, such as ACS, in high-risk patient populations most affected by these conditions would allow for timelier and more aggressively targeted preventive and therapeutic interventions in these patients.

2. Methods

2.1. Study aim

We aimed to investigate whether HCV infection is associated with hospital admissions for ACS events among hospitalized patients at the University of Maryland Medical Center (UMMC).

2.2. Study population

Our study examined patients admitted to inpatient medical and cardiac services at UMMC from November 2015 through December 2018. The hospital is a tertiary care facility in Baltimore, Maryland serving large numbers of indigent patients and a high percentage of high-risk patient demographic groups. Eligible subjects were at least 18 years old and admitted to UMMC at least once on the medical and/or cardiac services during the study period. The Institutional Review Board of the University of Maryland, Baltimore determined this study (HP-00083839) was not human subjects research and did not require review because study investigators did not receive any patient personal health identifying information nor had access to database linking de-identified data to patient identity.

2.3. Data collection

We obtained socio-demographic and clinical data of subjects from the Research Helping Advance Research By Organizing Resources Warehouse of the University of Maryland Medical Systems. Every inpatient admission encounter for every subject was obtained during the study period. The Helping Advance Research By Organizing Resources team extracted all study variables and all medical diagnoses listed in both the Problem List and Encounter Diagnosis for each admission encounter from subjects' electronic hospital medical charts, and provided de-identified data to the investigators.

2.4. Study variables

The primary outcome was hospital admissions for acute coronary syndrome (ACS), which was defined as myocardial infarction (MI) or angina using ICD-10 codes (I20-I25). The primary exposure was HCV infection, which was determined using ICD-10 codes (B17.9, B18.2, B19.20, K74.0) and positive total HCV antibody and positive HCV ribonucleic acid (RNA) results. For subjects with multiple encounters during the study period, all encounters were reviewed for presence of HCV infection and ACS. If a subject had at least one encounter with a positive HCV or ACS recording, the subject was recorded as having HCV infection or having experienced an ACS event, respectively. Covariates of interest included: age, sex, race, alcohol use, tobacco use, illicit drug use, diagnosis of hypertension, diagnosis of diabetes mellitus, human immunodeficiency virus (HIV) infection, body mass index (BMI), dyslipidemia (elevated total cholesterol, low-density lipoprotein, triglycerides, and decreased high-density lipoprotein, and family history of CHD. Diagnoses of diabetes mellitus, hypertension, and hyperlipidemia were identified using ICD-10 codes and medication use for each respective co-morbidity. HIV infection was defined using ICD-10 code and positive HIV antigen/antibody test or presence of an HIV viral load result. BMI values were calculated values in the medical charts. All covariates were identified using information recorded at time of hospital admission for the first hospital encounter.

HCV infection and hospitalization for ACS were expressed as binary variables (presence/absence of infection or event). Age was expressed as a categorical variable and classified as < 50 years, 50 to 64 years, or > 65 years of age. All other covariates were expressed as either binary (sex, diabetes mellitus, hypertension, hyperlipidemia, HIV infection, use of alcohol, tobacco, and illicit drugs) or categorical (race) variables.

2.5. Statistical analysis

We conducted a matched case-control study of 4446 patients with 5739 eligible visits. One patient was excluded due to missing data on all study variables of interest, and 68 were excluded due

to missing data on the exposure variable. An additional 17 patients were excluded for hospital admissions related to HCV conditions (infections associated with HCV and/or injection drug use, substance abuse non-infectious complications, and complications of compensated or decompensated cirrhosis). Cases were matched to controls (1:2) on sex, age, and race/ethnicity. Another five patients without race data were excluded. Matching was performed using simple random sampling without replacement to produce a matched random sample. We concatenated the matching variables to make a stratification indicator, which was utilized to select cases and controls randomly from each stratum. The final matched dataset comprised of 3368 patients with 4665 visits.

Clinical and demographic characteristics were compared between cases and controls and between those with and without HCV. 383 (11.4%) patients had HCV testing information available. The Chi-square test was used to assess significant associations, defined as *P*-values <0.20. Covariates with significant associations with case status and outcome were considered potential confounders and included in the final adjusted analysis. We used conditional logistic regression to examine the relationship between HCV infection and ACS, and odds ratio (OR) with 95% confidence intervals (CI) were reported. Alcohol use was selected a priori based on biological plausibility and assessed for modification of the effect of HCV on ACS since regular, heavy alcohol use can predispose to behaviors increasing risk of HCV infection and some studies suggest alcohol use may be another potential risk factor for cardiovascular disease. The order of covariates added into the adjusted model was determined by clinical relevance, convention, improvement of the model fit, and significance of change in OR (10%) from the unadjusted model. Significance was assessed at a p-value <0.05 using a two tailed test. Though HIV infection is an important clinical variable, it was not included in the analysis because of the small number of diagnoses identified (n=21). All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

We conducted a secondary analysis using propensity score matching with the Greedy method (1:1) to address concerns about residual confounding of select important factors associated with CVD. The propensity score included the following variables: age, race, sex, BMI, diabetes, hypertension, dyslipidemia, alcohol use, illicit drug use and current smoking status. When we used the 1:2 and 1:3 methods, there were cases that did not have sufficient matches.

3. Results

There were 3368 patients included in the final sample. Patients hospitalized for ACS cases were more likely to be current smokers, but less likely to have diabetes, hypertension, or illicit drug use compared to controls hospitalized for other reasons. Cases and controls had comparable BMI and hyperlipidemia (Table 1). Bivariate analysis showed significant associations between HCV and current smoking, hypertension, diabetes mellitus and BMI but no significant association between HCV and hyperlipidemia (data not shown). There was no association between hospitalization for having an ACS event in those with HCV infection compared to hospitalization for other conditions in the crude analysis (data not shown) or in adjusted models (OR 0.71, 95% confidence interval 0.45–1.11) in our primary analyses (Table 2). There was no modification of the effect of HCV on hospitalization for ACS by alcohol use (interaction term *P*-value $>.05$) (data not shown). Sensitivity analyses explored the impact of diabetes mellitus to the final model and it did not change the size of the estimate between HCV and ACS when excluded from the model (data not shown). The results of propensity score matching analyses were consistent with those of our primary analyses, showing no association between hospitalization for having an ACS event in those with HCV infection compared to hospitalization for other conditions (see Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A197).

Table 1

Description of demographic and clinical characteristics of hepatitis C virus-infected and uninfected patients.

Variable	Case N=1555 (33.33%)	Control N=3110 (66.67%)	*P* value[†]
Demographic characteristics, N (%)			
Sex			
Male	964 (61.99)	1928 (61.99)	1.0
Age, yr			
<50	198 (12.73)	396 (12.73)	1.0
50–64	671 (43.15)	1342 (43.15)	
≥65	686 (44.12)	1372 (44.12)	
Race/Ethnicity[*]			
White	850 (54.66)	1700 (54.66)	1.0
Black/African American	621 (39.94)	1242 (39.94)	
Other	84 (5.4)	168 (5.4)	
Current smoker[*]	347 (23.03)	343 (11.35)	<.0001
Alcohol use[*]	471 (32.13)	864 (29)	.03
Drug use[*]	195 (13.35)	254 (8.61)	<.0001
BMI[*]			
≥30	602 (39.09)	1286 (41.54)	.11
Clinical characteristics, N (%)			
Diabetes	555 (35.69)	1013 (32.57)	.03
Hypertension	1208 (77.68)	2586 (83.15)	<.0001
Hyperlipidemia	962 (61.86)	1906 (61.29)	.70
HIV	8 (0.51)	13 (0.42)	.64
HCV	31 (1.99)	75 (2.41)	.37

BMI=body mass index, HCV=hepatitis C virus, HIV=human immunodeficiency virus.
[†] *P* value derived from Chi Square testing.
[*] variables with missing data: Alcohol use n=220, Drug use n=255, Current smoker n=136, BMI n=29.

4. Discussion

Previous studies including heterogenous study designs that investigated the association between HCV infection and atherosclerotic events have produced mixed results. These studies compared HCV-infected persons to uninfected persons or HCV/HIV co-infected persons to HIV mono-infected persons (Table 3). Pothineni et al conducted a retrospective cohort study examining HCV-infected and uninfected subjects. Their study found that HCV seropositivity was an independent risk factor for incident CHD events.[5] In contrast, Forde et al found HCV positivity was not associated with increased rate of incident acute myocardial infarction (AMI).[7] In addition, Younossi et al found that chronic HCV infection was independently associated with congestive heart failure but not ischemic heart disease or stroke, and there was no association with cardiovascular disease (CVD) in almost 20,000 persons in the NHANES.[6] Finally, a recent study found that chronic HCV infection was associated with increased supply-demand mismatch type 2 AMI but not classical

Table 2

Adjusted association between hepatitis C virus status and hospitalization for acute coronary syndrome (total sample size = 4505, hospitalized acute coronary syndrome cases = 1494).

Variable	Odds Ratio (95% Confidence Interval)	*P* value
HCV Infection		
Uninfected	REF	
Infected	0.71 (0.45–1.11)	.13
Hypertension		
No	REF	
Yes	0.70 (0.60–0.83)	<.0001
Diabetes		
No	REF	
Yes	1.3 (1.14–1.49)	.0001
BMI		
<30	REF	
≥30	0.95 (0.83–1.08)	.4
Current Smoker		
No	REF	
Yes	2.43 (2.05–2.89)	<.0001

Adjusted for age, race/ethnicity and sex in the matching indicator.
BMI = body mass index, HCV = hepatitis C virus.

atheroembolic type 1 AMI, highlighting the importance of distinguishing between types of MI.[10] Our study found that infection with HCV was not associated with the odds of hospitalization for an ACS event compared to hospitalization for other conditions. This finding did not support the hypothesis that HCV infection is associated with ACS events among hospitalized patients and was consistent with some studies that showed similar results.[6,7] Relative to other studies, our study of 3368 subjects was smaller, and HCV infection was less prevalent (<2%) than most studies except the NHANES which reported 0.88% prevalence and ours included a larger percentage of Blacks and those diagnosed with hypertension. Conflicting results regarding the association between HCV infection and some form of IHD (CHD, ACS, angina, AMI, coronary artery disease) may be due to varying study designs, study populations, method of participant selection, methods of HCV and/or outcome definitions and assessments, lack of differentiation between MI types, or covariates and confounders included in adjusted analyses. Alternatively, it is possible that there is no association between HCV infection and ACS as shown in our study, and results from different studies may represent random error around the null hypothesis of no effect.

Our study also found that some traditional risk factors (diabetes, current smoker) were associated with significantly increased odds of hospitalization for an ACS event in our study population. These findings are consistent with the literature[5–8,10], suggesting that our study population is sufficiently valid to detect relevant associations between ACS and CVD factors. The literature has mixed findings regarding the association between BMI and CVD, and our study found that BMI was not associated with odds of hospitalization for ACS. Younossi et al found that obesity was an independent predictor of CVD in patients without chronic liver disease other than chronic hepatitis C infection,[6] but Pothineni et al found that obese HCV RNA positive patients had relatively lower odds of CHD than non-obese HCV RNA positive patients.[5] Lastly, our finding of decreased odds of hospitalization for an ACS event in those with hypertension was unexpected. This may have been due to the small number of HCV-infected patients in our study sample, misclassification of HCV exposure due to lack of a test being done, or misclassification of hypertension among HCV-infected patients since they are seen less frequently for care and therefore less likely to receive a diagnosis of hypertension. Further investigation into this relationship between HCV infection and hypertension should be conducted in larger prospective studies.

Our study had several limitations. First, our study was restricted to hospitalized patients rather than a population-based cohort, leading to selection bias of the study population. Nonetheless, the findings would be pertinent in high-risk, hospitalized patient populations and useful in that context. Second, as with all studies that rely on ICD codes, there may have been misclassification of HCV infection and/or ACS. To reduce potential for misclassification, we used both ICD codes and laboratory results to identify HCV infection and restricted the study population to patients admitted on general medicine and cardiac inpatient services; the ACS discharge diagnosis was more likely to be accurate on those services compared to others. Furthermore, selection of patients for AMI based on ICD codes has been shown to be associated with 94% sensitivity and 99% specificity, suggesting using ICD codes to ascertain AMI is reassuringly robust.[11] Third, the strikingly low prevalence of HCV infection in our study population compared to many previous studies may have affected the association between exposure and outcome. This likely contributed to the low power (<0.8) of our ability to detect the association between HCV infection and hospitalization for ACS events. Fourth, we likely missed diagnoses of HCV infection due to diagnosis and testing conducted outside of the study duration or outside the hospital setting in instances when the patient was unaware of their diagnosis or unable to communicate it to admitting teams. Fifth, we were unable to differentiate between prior (spontaneously cleared or treated), chronic, or acute HCV infection in our analyses due to the low number of RNA polymerase chain reaction test results available. The association between prior versus chronic versus acute HCV infection and ACS event may very well have been different and affected our study findings, and we may have included those who had already cleared infection in the exposure group. However, over 80% of those with HCV infection develop chronic HCV infection, and none of those with positive HCV RNA detectable values had negative HCV antibodies. In addition, we were unable to accurately capture data on liver disease stages or presence of cirrhosis as these data were not entered into the medical records systematically. Most patients were also missing laboratory values needed to systematically calculate fibrosis scores. Finally, though we could not establish a firm temporal relationship between HCV infection and ACS event from the database itself, the vast majority of HCV diagnoses represent chronic HCV infection. Therefore, it is reasonable to consider HCV diagnoses in the database as preceding the ACS event that occurred during hospitalization.

Our study also had important strengths. Our study population consists of large percentages of high-risk demographic groups that are often underrepresented in larger cohorts but are overrepresented in the HCV epidemic, making our study findings to be most applicable to this study population.[9] In addition, we undertook a careful analysis of all potential covariates for their suitability as confounders missing in previous studies investigating the relationship between HCV infection and ACS. Therefore, despite the potential selection and information biases, our study findings further inform the current debate about the association of HCV infection and ACS in high-risk patient populations.

Table 3

Summary of referenced studies and their limitations.

Study	Study Design	Sample Size	Exposure	Outcomes	Results	Limitation(s)	Addressing limitations in this study
Pothineni, N et al. (2014) doi: 10.1016/j.amjcard.2014.09.020	Retrospective cohort (2001–2013)	n = 24,484 HCV Ab+: 8251 HCV RNA+: 1434 Controls: 14,799	HCV infection (ICD-9)	Chronic stable angina, unstable angina, CAD, acute MI	HCV seropositivity (OR 1.32, 95% CI 1.09–1.60, $p < 0.001$) HCV RNA positivity (OR 1.59, 95% CI 1.13–2.26, $p < 0.001$)	Not adjusted for smoking status Not adjusted for family history of vascular disease	Adjusted for smoking status; found to have increased odds of hospitalization for ACS event Adjusted for family history of coronary heart disease as was a covariate of interest
Forde KA et al. (2012) doi: 10.1111/j.1365–2893.2011.01545.x	Retrospective cohort (1996–2008)	n = 76,477 HCV+: 4809 Controls: 71,668	HCV infection (Read diagnostic code scheme)	Primary: first diagnosis of MI from start of follow-up Secondary: composite outcome of either incident MI or revascularization procedure	No difference in MI incidence rates between HCV+ vs HCV- (1.02 vs 0.92 events per 1000 person-years; p = 0.7) HCV infection was not associated with an increase risk of incident MI (adjusted HR 1.10; 95% CI 0.67–1.83)	Lacks data regarding patient race/ethnicity Relies on diagnostic codes and/or free text mention of HCV, no data regarding HCV Ab+ or RNA+	Included race/ethnicity data in case matching to controls Determined presence of HCV infection via ICD-10 codes, Ab+, and RNA+
Younossi ZM et al. (2013) doi: 10.1111/ apt.12234	Retrospective cohort (1999–2010)	n = 19,741 HCV RNA+: 173 Controls: 19,568	HCV infection (NHANES database)	IHD, stroke, CHF	Chronic hepatitis C infection independently associated with CHF (OR 2.49, 95% CI 1.04–5.96) but not IHD (OR 0.53, 95% CI 0.20–1.40) or stroke (OR 0.58, 95% CI 0.16–2.02) No overall association with CVD OR (0.93 95% CI 0.47–1.81)	Relied on self-reported cardiovascular outcomes Majority of patients <65 years old and relatively healthy	Cardiovascular outcomes determined from EMR with diagnosis being made by cardiology and internal medical inpatient teams likely more reliable than self-reporting Wider age range, includes many more patients ≥65 years old
Williams-Nguyen J, et al. (2019) doi: 10.1093/aje/kwz236	Retrospective cohort (1998–2016)	n = 23,407 HCV RNA+: 2,280 Controls: 21,127	HCV infection in those with HIV (ICD-9)	Type 1 and Type 2 MI	HCV was associated with a 46% greater risk of Type 2 MI (adjusted HR 1.46, 95% CI 1.09–1.97) but not Type 1 MI (adjusted HR 0.87, 95% CI 0.58–1.29)	Included HCV RNA only performed in course of routine clinical care, missing cases of chronic HCV	Determined presence of HCV infection via ICD-10 codes, Ab+, and RNA+

Ab = antibody, CAD = coronary artery disease, CHF = congenital heart failure, CI = confidence interval, EMR = electronic medical record, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HR = hazard ratio, ICD = International Classification of Diseases, IHD = ischemic heart disease, MI = myocardial infarction, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio, RNA = ribonucleic acid.

Overall, we found there was no statistically significant association between HCV infection and hospitalization for ACS in our study population. Though our result did not support our hypothesis, it is consistent with some prior studies and may represent the true lack of association between HCV infection and ACS. We present results from a predominantly African American cohort and, given the relative paucity of data in this population and current conflicting literature in the field, this relationship warrants further investigation in future prospective cohort and/or interventional studies in this high-risk demographic group. It is important to delineate the relationship between HCV infection and ACS conclusively given the potential intersections of these significant public health conditions.

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