

2018-09-01

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## Repository Citation

Lynch, Shaina M.; Wilson, Sarah M.; DeRycke, Eric C.; Driscoll, Mary A.; Becker, William C.; Goulet, Joseph L.; Kerns, Robert D.; Mattocks, Kristin M.; Brandt, Cynthia A.; Bathulapalli, Harini; Skanderson, Melissa; Haskell, Sally G.; and Bastian, Lori A., "Impact of Cigarette Smoking Status on Pain Intensity Among Veterans With and Without Hepatitis C" (2018). *Quantitative Health Sciences Publications and Presentations*. 1228.  
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## **Keywords**

Hepatitis C, Smoking, Veterans, Tobacco, Pain, smoking, pain, veterans, hepatitis c virus, cigarette smoking

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## Impact of Cigarette Smoking Status on Pain Intensity Among Veterans With and Without Hepatitis C

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*Funding sources:* This work was supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, and Health Services Research and Development Nos. IIR 12-118, CIN 13-407, IIR 15-092, and LIPS 96-013.

*Disclosure:* The views expressed in this manuscript are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States Government.

*Conflicts of interest:* The authors have no conflicts to disclose.

*Prior presentations:* Presented, in part, as a poster at the 2016 American College of Gastroenterology Annual Scientific Meeting, October 14–19, 2016, Las Vegas, NV, USA.

### Abstract

**Objective.** Chronic pain is a significant problem in patients living with hepatitis C virus (HCV). Tobacco smoking is an independent risk factor for high pain intensity among veterans. This study aims to examine the independent associations with smoking and HCV on pain intensity, as well as the interaction of smoking and HCV on the association with pain intensity. **Design/Participants.** Cross-sectional analysis of a cohort study of veterans of Operations Enduring Freedom/Iraqi Freedom/New Dawn (OEF/OIF/OND) who had at least one visit to a Veterans Health Administration (VHA) primary care clinic between 2001 and 2014. **Methods.** HCV was identified using ICD-9 codes from electronic medical records (EMRs). Pain intensity, reported on a 0–10 numeric rating scale, was categorized as none/mild (0–3) and moderate/severe (4–10). **Results.** Among 654,841 OEF/OIF/OND veterans (median age [interquartile range] = 26 [23–36] years), 2,942 (0.4%) were diagnosed with HCV. Overall, moderate/severe pain intensity was reported in 36% of veterans, and 37% were current smokers. The adjusted odds of reporting moderate/severe pain intensity were 1.23 times higher (95% confidence interval [CI] = 1.14–1.33) for those with HCV and 1.26 times higher (95% CI = 1.25–1.28) for current smokers. In the interaction model, there was a significant Smoking Status × HCV interaction ( $P = 0.03$ ). Among veterans with HCV, smoking had a significantly larger association with moderate/severe pain (adjusted odds ratio [OR] = 1.50,  $P < 0.001$ ) than among veterans without HCV (adjusted OR = 1.26,  $P < 0.001$ ). **Conclusions.** We found that current smoking is more strongly linked to pain intensity among veterans with HCV. Further investigations are needed to explore the impact of smoking status on pain and to promote smoking cessation and pain management in veterans with HCV.

**Key words:** Hepatitis C; Smoking; Veterans; Tobacco; Pain

## Introduction

Hepatitis C virus (HCV) is the most common blood-borne infection in the United States [1] and disproportionately affects US veterans. Compared with the general US population, HCV is two to three times more prevalent among veterans [2]. Within the population of US veterans, HCV is linked to increased likelihood of chronic pain and diagnosed pain disorders. Specifically among veterans with HCV who use Veterans Health Administration (VHA) health care services, up to 67% of have a documented pain diagnosis [3]. Pain conditions vary and include musculoskeletal pain, fibromyalgia, arthritis, and peripheral neuropathy [4]. Chronic pain among those living with HCV has multiple notable harmful effects, including increased incidence of psychiatric symptoms, decreased quality of life, and health care costs [5–7]. Although the etiology and mechanisms of pain among people with HCV are not fully understood, it is possible that tobacco smoking may play a role. Notably, there is new evidence linking smoking to joint pain in patients with HCV [8]. This is a significant issue because veterans with comorbid HCV and chronic pain are likely to smoke [5]. Despite the potential connection between HCV, smoking, and pain, this area is relatively understudied among veterans with HCV.

Both pain and smoking are relevant health concerns for veterans of Operations Enduring Freedom/Iraqi Freedom/New Dawn (OEF/OIF/OND) [9]. More than one-third of veterans from this relatively young cohort report moderate to severe pain intensity [10], and national data indicate that persons age 20–40 years (the approximate age range of this veteran cohort) have the highest incidence rate of acute HCV infection [11]. Smoking may be a particularly salient risk factor for pain among OEF/OIF/OND veterans. In a recent study of this cohort, current smokers were more likely to present with high pain intensity compared with former and never smokers [10].

A number of factors likely affect pain intensity in the context of HCV, including liver functioning, HCV pharmacotherapy, access to and type of pain treatment (e.g., opioid medication), and mental health disorders. Multiple studies of veterans with HCV have indicated that pain intensity is less associated with biological disease indicators and more associated with psychological processes such as depression or pain catastrophizing [12]. Although there is a growing body of research characterizing the overlap and interconnection between HCV, pain, and mental health symptoms [5,13], far less attention has been paid to how smoking and HCV may interact to increase risk for pain.

Smoking is highly prevalent among veterans with HCV, and moreover, it is likely to be associated with pain intensity. Among veterans with HCV who use VHA health care services, tobacco use is the most common substance use disorder, with 66% reporting a history of

tobacco use [14]. High smoking rates in this group are especially troubling as cigarette smoking is generally associated with higher pain intensity and greater functional impairment [15,16]. It is generally hypothesized that while smokers utilize tobacco to cope with or reduce pain, smoking also increases risk for chronic pain [15,17].

Given the high rates and clinical importance of HCV, smoking, and chronic pain among OEF/OIF/OND veterans, we aimed to examine the association of smoking and HCV with pain intensity. We had two hypotheses: 1) smoking and HCV would both be independently associated with pain intensity and 2) the association of smoking and pain intensity would be significantly higher for veterans with HCV.

## Methods

### Study Design and Population

The OEF/OIF/OND roster is supplied to the VHA by the Department of Defense Manpower Data Center's (DMDC's) Contingency Tracking System. The roster contains all veterans who separated from OEF/OIF/OND military service and enrolled in VHA health care between October 1, 2001, and September 30, 2014 (N=1,063,973). Further descriptions of the Women's Veterans Cohort can be reviewed by cited manuscript [18]. Our analyses included veterans who had the following: 1) at least one primary care visit at VHA, 2) information available on smoking status (N=756,816), and 3) reported pain intensity proximal to smoking status (N=654,841). The VHA Connecticut Healthcare System Institutional Review Boards reviewed and approved this study.

### Data Source

Data on eligible veterans were linked to VHA administrative and clinical data contained within the Corporate Data Warehouse (CDW). These databases provide a record of inpatient and outpatient health care encounters and coded diagnostic conditions (based on the International Classification of Diseases, Ninth Revision [ICD-9]).

### Measures

#### Demographic Variables

Variables included sex, education (high school graduation or equivalent, above high school), race/ethnicity (black, Hispanic, white, unknown/other), age, service-connected disability (no service connection to 49% service connection, 50–100% service connection), and military characteristics including rank (e.g., officer) and branch (e.g., US Army).

### Dependent Variable: Pain Intensity

Veterans seen at VHA primary care clinics are asked for about their pain levels using a 0–10 numeric rating scale (NRS) [19]. The pain intensity question asks veterans to “rate your current pain on a 0 (no pain) to 10 (worst pain imaginable)” range, and the response is recorded in the veterans’ electronic medical records (EMRs). The highest current pain intensity score was kept for analysis (+/- 30 days of the most recent documentation of smoking status). Similar to previous methodology [19,20], current pain intensity was grouped dichotomously into none/mild (scores ranging from 0 to 3) or moderate/severe (scores ranging from 4 to 10).

### Independent Variables of Interest: Cigarette Smoking Status and HCV Diagnosis

For this study, we identified the most recent smoking status. Smoking status was determined using methodology from McGinnis et al. [21] that uses EMR Health Factors Smoking data from clinical reminders. Veterans were categorized as never, former, and current smokers using a key word algorithm (e.g., current smoker, never smoker, tobacco counseling). McGinnis found high agreement between EMR Health Factors smoking data and survey results [21].

HCV was identified if the veteran ever had any of the following ICD-9 codes: 070.41, 070.44, 070.51, 070.54, and V02.62.

### Covariates

In multivariate analysis, we selected the following a priori covariates: sex, age, race/ethnicity, pain-related diagnosis, and mental health diagnoses. Using existing methodology [22], pain-related diagnosis was determined via diagnostic codes for the following back pain conditions: joint disorders, osteoarthritis, back conditions, headache, cervicalgia, degeneration of lumbar, lumbosacral, or intervertebral disc, musculoskeletal/connective tissue disorders, and peripheral neuropathy. To identify these disorders, we used the following ICD-9 codes: 307.81, 307.89, 337.2x, 346, 356, 524.6, 710–719, 720–724, 725–739, 729.1, 784, 805, 806, 846, 847.

Mental health conditions were classified using Clinical Classifications Software ICD-9 codes from the Agency for Healthcare Research and Quality (AHRQ) [23]. We examined if patients had the following conditions based on their frequent comorbidity with painful conditions and HCV: anxiety disorders (i.e., anxiety disorder not otherwise specified [NOS], panic disorder, generalized anxiety disorder, agoraphobia with and without panic, other anxiety states); major depressive disorder; PTSD; and substance use disorder (combining alcohol use disorder and drug use disorder).

### Analysis

To compare sample characteristics by HCV diagnosis at the bivariate level, we used  $\chi^2$  tests and *t* tests. To examine the association of covariates and primary variables of interest with pain intensity, we used a series of logistic regressions that modeled the probability of moderate/severe pain intensity. Primary variables of interest included current smoking status (current smoker vs former/never smoker) and HCV diagnosis.

First, we examined unadjusted odds of reporting moderate/severe pain by each variable. Second, a multivariate logistic regression model was used to calculate the adjusted odds of moderate/severe pain with all variables of interest. Finally, we tested an interaction term for Smoking Status  $\times$  HCV Diagnosis and all other variables as above. Bivariate associations are reported as odds ratios (ORs), multivariate associations as adjusted ORs (AORs), and the results for the interaction test are reported as a Wald  $\chi^2$  statistic. All statistical analyses were performed using SAS, version 9.4 (SAS, Inc., Cary, NC, USA).

### Results

In this cohort of 654,841 OEF/OIF/OND veterans (median age [interquartile range]=26 [23–36] years), we identified 2,942 (0.4%) with an HCV diagnosis. More than one-third of the sample (37.6%) was classified as current smokers. Among all participants in the sample, 36.1% (N=236,672) reported a maximum pain intensity in the moderate to severe range. There were several differences between veterans with and without HCV at the bivariate level (Table 1). Compared with those without HCV, veterans with HCV were more likely to be white, older, male, and current smokers. Veterans with HCV were also more likely to report moderate to severe pain intensity and to have a pain diagnosis. Veterans with HCV were more likely to be diagnosed with major depressive disorder, anxiety disorder, PTSD, and substance use disorder.

In unadjusted analyses, all covariates and variables of interest were significantly associated with higher odds of reporting moderate to severe pain intensity (Table 2). Compared with veterans without HCV, the unadjusted odds of reporting moderate/severe pain were 1.82 times higher (95% confidence interval [CI] = 1.70–1.96) for those with HCV. Compared with nonsmokers, the unadjusted odds of reporting moderate/severe pain were 1.32 times higher (95% CI = 1.30–1.33) for veterans who smoked.

Results were similar after adjusting for other covariates (Table 2). In adjusted analyses, all variables were significantly associated with a higher odds of reporting moderate/severe pain. Compared with veterans without an HCV diagnosis, the adjusted odds of reporting moderate/severe pain were 1.23 times higher (95% CI = 1.14–1.33) for those with HCV. In comparison with

**Table 1.** Sample Characteristics by HCV Diagnosis

	HCV Diagnosis (N = 2,942)	No HCV (N = 651,899)	Total (N = 654,841)	P value
Age, median (IQR), y	28 (23–43)	26 (23–36)	26 (23–36)	<0.0001
Gender				<0.0001
Women	9.8	12.7	12.7	
Men	90.2	87.3	87.3	
Race (missing 7,903), %				<0.0001
White	68.1	64.5	64.5	
Black	15.7	17.5	17.5	
Hispanic	12.0	11.9	11.9	
Other	4.2	6.1	6.1	
Education (missing 171), %				<0.0001
Less than high school	2.3	1.3	1.3	
High school or higher	97.7	98.7	98.7	
Marital status (missing 40,941), %				<0.0001
Married	42.3	49.3	49.3	
Not married	57.6	50.7	50.7	
Rank, %				<0.0001
Enlisted	97.1	93.3	93.3	
Officer/warrant	2.9	6.7	6.7	
Branch, %				<0.0001
Army	71.9	61.3	61.3	
Air Force	6.8	10.5	10.5	
Marine Corps	9.1	14.6	14.6	
Navy	12.2	13.6	13.6	
At least 50% SC disability, %	60.7	41.8	42.9	<0.0001
Pain intensity, median (IQR)	4 (0–7)	1 (0–5)	1 (0–5)	<0.0001
Pain intensity, %				<0.0001
None to mild (0–3)	49.3	63.9	63.8	
Moderate to severe (4–10)	50.7	36.1	36.1	
Pain diagnoses, %	85.8	70.3	70.4	<0.0001
Mental health diagnoses, %				
Major depression	28.9	11.1	11.2	<0.0001
PTSD	62.8	33.5	33.6	<0.0001
Anxiety	39.3	18.7	18.8	<0.0001
Substance use	57.3	15.0	12.8	<0.0001
Smoking status, %				<0.0001
Current	58.2	37.5	37.6	
Former	17.0	17.2	17.2	
Never	24.8	45.3	45.2	

HCV = hepatitis C virus; IQR = interquartile range; PTSD = post-traumatic stress disorder; SC = service-connected.

veterans who did not currently smoke, the adjusted odds of reporting moderate/severe pain were 1.26 times higher (95% CI = 1.24–1.28) for smokers. There was a significant Smoking Status  $\times$  HCV Diagnosis interaction (Wald  $\chi^2$  (1) = 4.86,  $P$  = 0.03). To probe the interaction, the adjusted probability of reporting moderate/severe pain was calculated by smoking status and HCV diagnosis. Among veterans without HCV, smoking had a modest effect on the probability of reporting moderate/severe pain (adjusted OR = 1.26,  $P$  < 0.001). However, among veterans with HCV, smoking had a significantly larger effect on moderate/severe pain (adjusted OR = 1.50,  $P$  < 0.001). Given unequal group prevalence of psychiatric comorbidities by smoking status and HCV diagnosis, a graph was created that shows the probability of moderate/severe pain by smoking status and HCV diagnosis, which also takes into account group differences in substance use, depression, and PTSD diagnoses (Figure 1). After accounting for the prevalence of substance use,

depression, and PTSD among veterans with HCV, the adjusted probability of moderate/severe pain was 51.8% (95% CI = 0.494–0.543).

## Discussion

This study used a national data set of veterans returning from recent wars (OEF/OIF/OND) and demonstrated that, compared with veterans without HCV, veterans with HCV were more likely to report moderate/severe pain intensity and to be current smokers. Although the association between pain and smoking was significant and positive for veterans with and without an HCV diagnosis, the association was significantly higher for patients with an HCV diagnosis than those without. The association between pain intensity and smoking status has been previously reported, but, to our knowledge, this study is the first to report this association in veterans with HCV. Due to the high burden of chronic pain conditions in

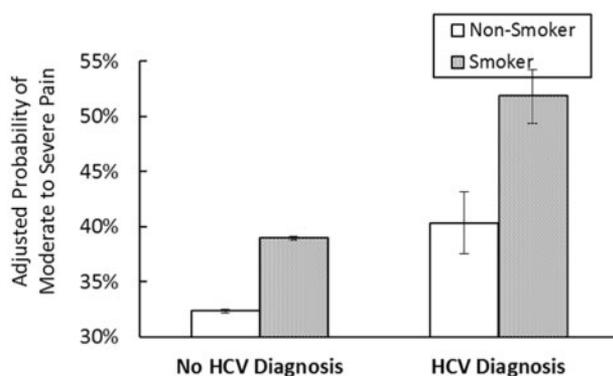
**Table 2.** Logistic Regression Models Predicting Moderate to Severe Pain

Variable	Unadjusted		Adjusted*	
	OR <sup>†</sup>	95% CI	OR <sup>†</sup>	95% CI
Age	1.01	1.01–1.01	1.01	1.01–1.01
Nonwhite (ref: white)	1.22	1.21–1.23	1.26	1.25–1.28
Male (ref: female)	1.05	1.03–1.07	1.01	0.99–1.02
Substance use disorder	1.74	1.72–1.77	1.17	1.15–1.19
Major depressive disorder	2.03	1.99–2.06	1.39	1.37–1.42
PTSD	2.35	2.33–2.38	2.11	2.09–2.14
Current smoker	1.32	1.30–1.33	1.26	1.25–1.28
Hepatitis C diagnosis	1.82	1.70–1.96	1.23	1.14–1.33

CI = confidence interval; OR = odds ratio; PTSD = post-traumatic stress disorder.

\*Multivariate logistic model adjusted for all other variables.

<sup>†</sup> $P < 0.001$  for all modeled effects.



**Figure 1.** Probability of moderate to severe pain by smoking status and hepatitis C virus diagnosis, taking into account group differences in psychiatric comorbidity. Adjusted probability accounts for differences in group means in psychiatric diagnoses (depression, post-traumatic stress disorder, and substance use disorders) and assumes omnibus group means among all other covariates. HCV = hepatitis C virus.

patients with HCV, the study highlights the need to understand the impact of smoking status on pain intensity and then develop interventions to promote smoking cessation and pain management in this younger veteran population.

In this study, patients with HCV had higher rates of smoking compared with patients without HCV (58% vs 37%). Other studies have found even higher rates of smoking among patients with HCV [6,7,11,24]. In a recent survey of veterans with HCV, tobacco use was found to be the most common substance use disorder, with 66% of patients reporting a history of tobacco use [14]. Unfortunately, there are numerous barriers to smoking cessation for patients with HCV. In a qualitative study of patients with HCV, almost a quarter (22.5%) believed that smoking “helped fight the HCV” [25]. Patients with HCV would benefit from a smoking cessation program that highlights the negative consequences of smoking (such as a pain condition) related to their disease.

In this cohort of younger veterans, patients with HCV had higher rates of moderate/severe pain intensity (51% vs 36%) and pain conditions (86% vs 70%) compared with veterans without HCV. In previous studies, more than 80% of patients with HCV reported pain symptoms [5] and over two-thirds (71%) of patients with HCV reported joint pain [8]. Other studies have reported higher rates of fibromyalgia [26], peripheral neuropathy [27], and rheumatoid arthritis [28] among patients with HCV. The mechanism for HCV increasing musculoskeletal conditions remains unclear but might include direct invasion of the virus into the synovial tissue, an autoimmune response, and immune complex deposition [29]. More research is needed to understand whether treatments for HCV improve these painful conditions.

In the multivariate model, mental health disorders were associated with greater odds of reporting higher pain intensity, which is consistent with previous literature illustrating the association between psychological distress and pain [30,31]. Morasco et al. found that depression severity was the most significant predictor of both pain intensity and pain functioning in patients with HCV [12]. Adams and colleagues found that patients with HCV (43%) had clinically significant symptoms of depression and 58% had chronic pain [32]. In a study examining quality of life in patients with HCV, both smoking and alcohol use were associated with depression, fatigue, difficulty sleeping, and loss of interest in sex [7]. Previous studies have found that patients with HCV report using alcohol to cope with symptoms of PTSD and depression [33]. Clinicians should be aware of the higher rates of mental health disorders among patients with HCV and incorporate treatment plans that support mood, reduce distress, and promote pain coping accordingly. Prior interventions among patients with HCV have focused on cognitive behavioral self-management and exercise interventions to improve quality of life in areas such as pain intensity, depression, mood, and vitality [34,35].

This study has particular limitations. The cross-sectional study design limits our capacity to determine a temporal order of variables and to examine causation. The study results may be specific to veteran populations but less applicable to other clinical populations. We relied on an algorithm to determine self-reported smoking status, though we note that McGinnis et al. have validated this measure [21]. A single-item measure of pain intensity does not account for the full dynamics of pain in its quality, duration, and location [19]. Although prior research has suggested using an average measure of pain intensity because of short-term variability [36], we used the highest pain intensity measure that was +/- 30 days from the most recent smoking status to select these variables close in time. Using ICD-9 coding in our study has the potential to undercount comorbidities if providers did not code them in the VHA EMR.

Among veterans with HCV, this study illustrates the association between smoking status and pain. Smoking has a strong impact on the health of young veterans; smoking cessation and prevention programs need to start earlier in the military. As more patients with HCV undergo curative therapy, clinicians will need to refocus their attention on morbidities and mortalities associated with other chronic conditions such as smoking. Persons with HCV and chronic pain may be using smoking as a way to cope with or reduce pain and may experience more barriers to smoking cessation. Our research suggests that it may be important to provide more patient education about the links between smoking and pain, target smoking cessation, and provide assistance to manage chronic pain for veterans with HCV. Future research should examine the association of pain and smoking in veterans who have undergone curative therapy for HCV.

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