HHS Public Access

Author manuscript

Hepatology. Author manuscript; available in PMC 2017 November 07.

Published in final edited form as:

Hepatology. 2015 March ; 61(3): 802–811. doi:10.1002/hep.27422.

Predictors of Poor Mental and Physical Health Status among Patients with Chronic Hepatitis C Infection: the Chronic Hepatitis Cohort Study (CHeCS)

Joseph A. Boscarino, PhD, MPH[1], **Mei Lu, PhD**[2], **Anne C. Moorman, MPH**[3], **Stuart C. Gordon, MD**[2], **Loralee B. Rupp, MPH**[2], **Philip R. Spradling, MD**[3], **Eyasu H. Teshale, MD**[3], **Mark A. Schmidt, PhD**[4], **Vinutha Vijayadeva, PhD, MPH**[5], and **Scott D. Holmberg, MD, MPH**[3] **for the Chronic Hepatitis Cohort Study (CHeCS) Investigators***

[1]Geisinger Health System, Danville, PA

[2]Henry Ford Health System, Detroit, MI

[3]Division of Viral Hepatitis National Center for HIV, Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA

[4]Kaiser Permanente-Northwest, Portland OR

[5]Kaiser Permanente-Hawaii, Honolulu, HI

Abstract

Aims—Our objective was to assess the extent and risk factors for depression and poor physical health among patients with chronic hepatitis C virus (HCV) infection.

Methods—We surveyed HCV-infected patients seen at four large healthcare systems participating in the Chronic Hepatitis Cohort Study (CHeCS). Survey data included demographics, depression and physical health measures, substance use history, current social support, recent stressor exposures, and, from the electronic medical record, treatment history, and Charlson Comorbidity Index scores.

Results—There were 4,781 respondents, who were a mean of 57 years old, 71% White, and 57% male. Altogether, 51.4% reported past injection drug use, 33.9% were current smokers, and 17.7% had abused alcohol in the previous year. Additionally, 47.4% had been previously treated for HCV

Please address correspondence to: Joseph A. Boscarino, PhD, MPH, Center for Health Research, Geisinger Clinic, 100 N. Academy Avenue, M.C. 44-00, Danville, PA 17822, 570.214.9622 (phone), 570.214.9451 (fax).

*The CHeCS Investigators include the following investigators and sites: Scott D. Holmberg, Eyasu H. Teshale, Philip R. Spradling, and Anne C. Moorman, Division of Viral Hepatitis, National Centers for HIV, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia; Stuart C. Gordon, David R. Nerenz, Mei Lu, Lois Lamerato, Loralee B. Rupp, Nonna Akkerman, Nancy Oja-Tebbe, Chad M. Cogan, and Dana Larkin, Henry Ford Health System, Detroit, Michigan; Joseph A. Boscarino, Zahra S. Daar, Joe B. Leader, and Robert E. Smith, Geisinger Health System, Danville, Pennsylvania; Cynthia C. Nakasato, Vinutha Vijayadeva, Kelly E. Sylva, John V. Parker, and Mark M. Schmidt, Kaiser Permanente- Hawaii, Honolulu, Hawaii; Mark A. Schmidt, Judy L. Donald, and Erin M. Keast, Kaiser Permanente- Northwest, Portland, OR.

Ethical considerations: The investigation followed the guidelines of the U.S. Department of Health and Human Services regarding protection of human subjects. The study protocol was approved and renewed annually by each participating institution's institutional review board.

Conflict of interests: The authors have no conflict of interests associated with this research study.

A version of this paper was presented at the HMO Research Network National Conference, Phoenix, AZ, April 2014.

and 14.8% had a 12-week sustained viral response (SVR) following HCV therapy. Overall, 29.7% of patients met criteria for current depression and 24.6% were in poor physical health. In multivariate analyses, significant predictors of depression and poor health included: male gender (vs. female, OR, 0.70 and 0.81), Black race (vs. white, ORs, 0.60 and 0.61), having education less than high school (vs. college, ORs, 1.81 and 1.54), being employed (vs. not, ORs, 0.36 and 0.25), having high life stressors (vs. low, ORs, 2.44 and 1.64), having low social support (vs. high, ORs=2.78 and 1.40), and having high Charlson scores (vs. none, ORs=1.58 and 2.12). Achieving a 12- week SVR was found to be protective for depression.

Conclusions—This large survey of US HCV patients indicates the extent of adverse health behaviors and mental and physical comorbidities among these patients.

Keywords

Hepatitis C; Depression; Health Status; Quality of life; Risk Factors

Introduction

Currently, an estimated 2.7 million persons in the United States have chronic hepatitis C virus (HCV) infection.[1] Despite its prevalence, more needs to be learned about the spectrum of disease, access to care, effectiveness of therapies, and the quality of life for persons living with HCV infection. To assess the impact of chronic hepatitis infection, the Chronic Hepatitis Cohort Study (CHeCS) study is being carried out to assess the burden of care, modes of transmission, effectiveness of hepatitis screening, barriers to care, and appropriate treatments and their impact on mortality, morbidity and the quality of life.[2, 3] As part of CHeCS, surveys were conducted among all chronic hepatitis C patients known to be alive at the time of the survey.[4] The purpose of the survey was to assess hepatitis risk factors, treatment exposures, additional demographic variables, and key psychosocial measures in the course and outcome of chronic hepatitis disease, data important for public health and medical management of HCV disease.

The focus of the current study is to assess the quality of life of patients with chronic hepatitis C infection, especially the prevalence of current depression and poor health status as these relate to HCV treatment history and the course of disease,[5–9] in the largest sample of US patients to date. This research was guided, in part, by a psychosocial-stressor model used in previous investigations.[10, 11] This conceptualization supposes that exposure to environmental stressors and/or the availability of psychosocial resources impact health outcomes.[12–15]

Methods

The CHeCS study methods have been previously described in detailed elsewhere.[2, 3] Briefly, the cohort was created based on electronic health records (EHRs) of patients 18 years or older who had healthcare services provided between January 1, 2006 and December 31, 2010 at one of four sites: Geisinger Health System, Danville, PA; Henry Ford Health System, Detroit MI (data coordinating center); Kaiser Permanente-Northwest, Portland, OR; and Kaiser Permanente-Hawaii, Honolulu, HI. The electronic data collected included patient

demographic information, medical encounter data, laboratory results, diagnosis and procedure data, and liver biopsy results. Electronic data used in this analysis were available retrospectively to January 1997 from the Detroit and Portland sites, to January 1998 from the Hawaii site, and to January 2001 from the Danville site.[2, 3]

Patients meeting laboratory and diagnosis criteria for chronic hepatitis C were included in the cohort and were eligible for the survey, if they were known to be alive at the time of the survey (2011–2012). The CHeCS survey was designed to collect data on patient demographics, reported hepatitis risk factors, comorbidities, physical and mental functioning, use of alcohol and other psychoactive substances, treatment for alcohol and drug abuse, and on chronic hepatitis treatment history.

Cohort selection

Algorithms for inclusion in the chronic hepatitis cohorts were developed and applied to the EHR data of patients aged 18 years or older from all sites with any health care utilization between January 1, 2006 and December 31, 2010.[2, 3] Complete observation time for each patient was determined to be time from first evidence of hepatitis infection in the EHR including retrospective data prior to January 1, 2006, until either the last health system encounter or December 31, 2010. Patients were included in the hepatitis cohorts based on fulfillment of a combination of laboratory-based and ICD-9-based criteria discussed elsewhere.[2, 3] Trained medical abstractors reviewed the EHRs to collect liver biopsy results, outside system laboratory reports, and detailed antiviral therapy data on all patients receiving treatment during 2001–2010. Electronic medical charts flagged by abstractors as missing evidence of chronic HCV infection were reviewed under the supervision of a hepatitis clinician using clinician-developed criteria. Cases for which chronic HCV infection had been ruled out were excluded from the study cohort.

Survey Data Collection

Altogether, we examined the records of 2,143,369 patients aged ≥18 years in the four participating health systems that had one or more services provided between January 1, 2006 and December 31, 2010. Of these patients, 12,259 patients met the hepatitis C cohort inclusion criteria.[2, 3] Median time under observation for patients in the HCV cohort was 4.3 years (range 0–18 years), for a total 90,566 person-years of observation. Across all sites approximately three-quarters of the chronic hepatitis C patients were born between 1945 through 1964.[2, 3] The payer status of patients varied by site, with the percentage of patients using only public insurance (Medicaid or Medicare only) ranging from 2.3% in Portland to 50.4% in Danville and the percentage of uninsured ranging from 3.9% in Danville to 10.0% in Detroit.

Of the 12,259 patients who met the hepatitis C cohort inclusion criteria, 7,756 were known to be alive and not institutionalized and surveyed by mail and telephone during 2011–2012. Up to 8 survey attempts were initiated in order to complete an interview with each patient. A small incentive was offered at each site to encourage survey response. Patients who were found to be deceased, incarcerated, in long-term care institutions, or who had invalid

addresses or disconnected telephone numbers were excluded from the denominator. The survey was conducted in English only.

Quality of Life Measures

For the current study we included two quality of life measures -- the PHQ-8 scale [16, 17] and the SF-8 scale.[18, 19] The PHQ-8 scale assesses current depression and has been clinically validated in population health research.[16, 17] A PHQ-8 score of > 10 has high sensitivity and specificity for both the presence of major depression and for the presence of any depressive disorders and was the clinical cut-point used to define current depression.[16]

The SF-8 scale evolved from the Medical Outcome Study program, which originally included the Short-Form-36 (SF-36) instrument,[20–22] now widely used in clinical research.[23, 24] The SF-8 is based on items related to physical and mental health status and only has 8 items,[24] but these measures have the same metric as the SF-36 scale, whereby the average population mean for the SF-8 is designed to be 50, with a standard deviation 10 for the US population.[24] We used the current study population's 25th percentile as the cut-off score norm for the present study (i.e., means of 35.6 and 38.7, respectively, for physical and mental health). These score means for physical and mental health status are consistent with the 25th percentile norms for patients with advanced cancer or severe liver disease.[23] The SF scales results are typically reported in terms population benchmarks or norms.[20–24]

Other Study Measures

Other survey data included demographic information (age, race/ethnicity, marital status, education level, employment status, county of birth) and self-reported psychoactive substance use (cigarette smoking, history of heavy alcohol use, history of alcohol or drug abuse treatment, and history of injection of illicit drugs). The survey also collected data on current alcohol dependence using the AUDIT-C scale,[25, 26] exposure to recent psychological stressors,[13, 27] and level of social support.[13, 28] In addition, the survey contained HCV-specific questions, including questions related to having visited a liver or hepatitis specialist, being prescribed hepatitis drugs, having stopped or changed hepatitis medication in the past 12 months, and use of hepatitis medications in the past 4 weeks. Household income for survey respondents was geo-coded and based on 2010 US Census data.[29] Patient data from the electronic health record also included gender, history of liver transplantation, the presence of decomensated or end stage liver disease, HCV genotype, use of pegylated interferon, use of ribavirin, and evidence of 12 or more week sustained viral response (SVR) following therapy. From the EHR, scores for the Charlson Comorbidity Index were also calculated.[30–32] Based on previous research, the Charlson Comorbidity Index was used to categorize patients into no score, low score, moderate score, or high score results.[33]

Statistical Methods

For population descriptive statistics, we used the exact binomial method to create 95% confidence intervals around study point estimates (Table 1). Logistic regression modeling was also used to assess individual risk factors associated with poor quality of life, including the presence of depression and/or poor physical or mental health status, controlling for other risk factors and confounders. The variables with $p < 0.20$ in bivariate analyses were included

as candidate measures in the initial multivariable models. Using forward stepwise selection, the final models retained only risk factors with $p < 0.10$. Statistical analyses were conducted using Stata version 13.1[34]. Because the PHQ-8 depression scale was highly correlated with SF-8 mental health component scale ($r = 0.80$) and both these scales assess depression, the SF-8 mental health results are not presented in the current study, but are available upon request. All logistic regression models shown were adjusted for the four study sites.

Ethical Conduct and Funding of Study

The study was funded by donations from pharmaceutical companies to the CDC Foundation; granting corporations did not have access to CHeCS data and did not contribute to data analysis or writing of manuscripts. The study protocol was reviewed by an Institutional Review Board and approved by the Office for Human Research Protections at each participating study site.

Results

Overall, 4,781 surveys were completed, representing ~60% of those surveyed. Altogether, 156 of these 4,781 respondents (~3%) were HBV or HIV co-infected. Comparison of survey respondents to non-respondents indicated that survey respondents tended to be female, white, older, privately insured, and to have had HCV treatments ($p < 0.001$). The survey respondents were mainly male (57%), a mean age of 56.7 years old, were mostly White (71%), and often married (50.4%) (Table 1). In addition, 20.4% were college graduates, 47.9% were employed full-time or part-time, 61.1% were privately insured, 51.4% had a history of injection drug use (IDU), and substantial proportions were current cigarette smokers (33.9%) (Table 1). While 7.2% reported drinking alcohol 4+ times per week, per AUDIT-C scale, 17.7% were classified as current alcohol abusers. Many (47.4%) had a history of treatment for HCV, and 14.8% had a 12-week sustained viral response (SVR) to treatment. A total of 29.7% of patients were depressed on the PHQ-8 scale and, by study design, 24.6% were classified as having poor physical health on the SF-8 scale (Table 1).

In bivariate analyses, current depression was strongly statistically associated with many demographic, social, and medical status variables (Table 2): with history of injection drug use; alcohol rehabilitation; drug abuse treatment; being a current smoker; and with not having private healthcare insurance. Depression was also associated with exposure to stressful life events in the past year, having lower social support in the past year, currently receiving HCV treatment, and higher scores on the Charlson Comorbidity Index. Finally, those achieving12-week sustained virologic response from previous HCV therapy (i.e., cured) were significantly less likely to be depressed (Table 2).

In multivariate logistic regression analysis, the strongest predictors of current depression (p-values < 0.001) were current employment, moderate or high stressful life events, and low or moderate social support (Table 2) However, having achieved a SVR from antiviral therapy was protective against being depressed (OR = 0.72, $p = 0.008$).

In bivariate analyses, poor physical health measured on the SF-8 scale was also significantly associated with a number of demographic and socioeconomic factors (p-values < 0.001),

including marital status, income, education, employment status, and health insurance status (Table 3). Poor physical health was also significantly associated with exposure to stressful life events, social support level, having seen a hepatologist, having a liver transplant, and Charlson Comorbity score. Patients with decompensated or end stage liver disease more often had poor physical health, but patients who took anti-viral drugs, either pegylated interferon or ribavirin in the past, more often reported better physical health. Finally, in the bivariate analyses, having achieved sustained virologic response from previous anti-HCV therapy was also associated with better physical health (Table 3).

In general, multivariate analysis confirmed the significant statistical associations seen in the bivariate analysis (Table 3); namely non-White race was protective, having lower income was a risk factor, being employed was protective, and that having higher stressful life events and lower social support were risk factors for poor health. Additionally, not having private health insurance was associated with poor health and having received care from a hepatologist was protective against poor health (Table 3). However, in multivariate analyses, having achieved sustained virologic response from anti-HCV therapy was not associated with better physical health.

Discussion

To our knowledge, this study represents one of the largest surveys of diagnosed chronic hepatitis C patients in the United States and provides insights into their mental and physical health and their comorbidities. As might be expected, both depression and physical health were associated with unemployment, higher stressful events, lower social support, and higher Charlson Comorbidity scores. Achieving sustained virologic response (SVR) from therapy was protective against depression, and achieving SVR was associated with better physical health in bivariate analyses, but otherwise HCV treatment did generally not affect current mental or physical health status in multivariate analysis, once other covariates were controlled. A notable exception was that those currently on “any” HCV medication had a tendency to be depressed (Table 2, OR=1.58, p = 0.011), but this did not appear to be associated with currently taking interferon medications, since the latter was not associated with depression (χ^2 = 0.018, p=0.84). However, the latter association is likely confounded by the time lag between EHR data collection and survey self-report. Nevertheless, in total, these data reflect wide comorbidities in those with chronic hepatitis C. This survey also provides some data not previously reported for a large HCV-infected population, such as the high current rates of cigarette smoking and current alcohol abuse among these patients. Such substance use, especially as they affect disease progression and outcomes, need to be incorporated in analyses of HCV patients’ morbidity and mortality.

Similar to what has been previously reported for HIV disease,[35, 36] it was anticipated that quality of life status of patients with chronic HCV infection would be associated with socio-demographic factors, treatment history, and disease progression status.[5–7, 37]. Our assumption was that better understanding of the psychosocial impact of this disease, knowledge of patients’ psychosocial responses to treatment, and the use of psychological interventions would likely result in better patient outcomes over time.[38–41] Our study of depression and physical health in these patients was guided, in part, by a “psychosocial-

stressor" model used in previous investigations.[10, 11] This model suggests that exposure to psychosocial stressors and/or the availability of psychosocial resources, including socioeconomic resources, are important and can significantly impact health outcomes.[12–15]

As was seen, 29.7% of HCV patients met criteria for current depression on the PHQ-8 scale and 24.6% are classified as having poor current physical health on the SF-8 scale. By comparison, in general population surveys, only about 9% have current depression using the PHQ-8 with a cut-point of ≥ 10.[16] Similar findings are true for SF-8 scale: The 25th percentile cut-point used to define poor physical health in the current study population (i.e., T-score ≤ 35.55), is typically the population percentile score reported for advanced cancer patients and those with severe liver disease.[23] The survey respondents studied mirrored the population of diagnosed HCV patients both in and out of care: [2] about half (51.4%) acknowledged previous injection drug use and about half are not currently employed (52.1%). It is also noteworthy that almost half of survey respondents had a history of HCV treatment (47.4%), 14.9% had stopped HCV treatments in the past 12 months, and 14.8% had experienced a 12-week SVR at some point, which is indicative of a HCV cure. Conversely, for those who did not generally achieve SVR, 5% have decompensated or end-stage liver disease, and 6% have had a liver transplant.

Both having chronic HCV infection and initiating interferon-based therapy, are known to be associated with depression.[5, 37] Further, patients' functional health status and work productivity have been recently reported to be more adversely affected by pegylated interferon treatments, than interferon-free treatments.[6, 42] However, achieving SVR was associated with improved emotional well-being—at least the absence of depression—in these patients. Conversely, there appeared to be little physical or mental health benefit for those who did not achieve SVR, for whatever reason, after starting antiviral therapy.

This study has some limitations. First, this study was mostly based on self-reported survey data and, thus, is subject to response biases. However, interview remains the only practical way to assess many of the elements examined in this survey of thousands of HCV patients, such as feelings of depression, stressful life events, social support, or substance misuse. Second, the survey response rate was only about 60%, after patients who were deceased, incarcerated, in long-term care institutions, or who had invalid addresses or disconnected telephone numbers were excluded from the study.[4] Still, those responding did not differ from the overall CHeCS cohort in demographic characteristics.[2] However, as noted, females, older persons, whites, those with a history of HCV treatments, and those with private insurance were more likely to complete the survey. This response bias may have affected our study results. In addition, the majority of those with a history of HCV treatment (~70%), were more likely to have compensated cirrhosis vs. being non-cirrhotic. Third, the survey was conducted in English only, which likely excluded some minority ethnic groups. Fourth, this study was cross-sectional and, therefore, causal inference is limited. For example, the finding reported for SVR and depression may be due to the fact that those with lower levels of depression may be more likely to adhere to treatment and, thus, achieve SVR. Fifth, we included 156 patients (~3%) who were HBV or HIV co-infected in our study and this may have biased our results, although we found little evidence of this in our analyses. Finally, the external validity of this study may be limited due to the fact that the research was restricted

to four study sites in the US, although these were large and geographically and demographically diverse sites representing well over 2 million US adults.

In conclusion, the impact of many behavioral, psychosocial, and treatment factors on functional mental and physical health status in chronic HCV patients is complex. We expect that even with the advent of interferon-free all oral HCV treatments, psychosocial and socioeconomic factors will continue to be an important consideration in assessing patient outcomes, risks, and costs.[41, 43, 44]

Acknowledgments

Financial support: CHeCS is funded by the CDC Foundation, which currently receives grants from AbbVie, Janssen Pharmaceuticals, Inc., and Vertex Pharmaceuticals. Past funders include Genentech, a Member of the Roche Group. Current and past partial funders include Gilead Sciences and Bristol-Myers Squibb. Granting corporations did not have access to CHeCS data and did not contribute to data analysis or writing of this manuscript.

References

1. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med. 2014; 160:293–300. [PubMed: 24737271]
2. Moorman AC, Gordon SC, Rupp LB, et al. Baseline Characteristics and Mortality Among People in Care for Chronic Viral Hepatitis: The Chronic Hepatitis Cohort Study. Clin Infect Dis. 2013; 56:40–50. [PubMed: 22990852]
3. Spradling PR, Rupp L, Moorman AC, et al. Hepatitis B and C virus infection among 1.2 million persons with access to care: factors associated with testing and infection prevalence. Clin Infect Dis. 2012; 55:1047–1055. [PubMed: 22875876]
4. Centers for Disease Control and Prevention (CDC). Locations and reasons for initial testing for hepatitis C infection--chronic hepatitis cohort study, United States, 2006–2010. MMWR Morb Mortal Wkly Rep. 2013; 62:645–648. [PubMed: 23945771]
5. Smith KJ, Norris S, O'Farrelly C, O'Mara SM. Risk factors for the development of depression in patients with hepatitis C taking interferon-alpha. Neuropsychiatr Dis Treat. 2011; 7:275–292. [PubMed: 21654873]
6. Younossi ZM, Stepanova M, Henry L, et al. Effects of Sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. Clin Gastroenterol Hepatol. 2013 Dec 6. [Epub ahead of print].
7. Strauss E, Porto-Ferreira FA, de Almeida-Neto C, Teixeira MC. Altered quality of life in the early stages of chronic hepatitis C is due to the virus itself. Clin Res Hepatol Gastroenterol. 2014; 38:40–45. [PubMed: 24239318]
8. Matsushita H, Ikeda F, Iwasaki Y, et al. Assessment of health-related quality of life and how it predicts the outcome of pegylated interferon and ribavirin therapy for chronic hepatitis C. J Gastroenterol Hepatol. 2014; 29:337–343. [PubMed: 23869873]
9. Bezemer G, Van Gool AR, Verheij-Hart E, et al. Long-term effects of treatment and response in patients with chronic hepatitis C on quality of life. An international, multicenter, randomized, controlled study. BMC Gastroenterol. 2012; 12:11-230X-12-11. [PubMed: 22292521]
10. Boscarino JA, Adams RE. PTSD onset and course following the World Trade Center disaster: findings and implications for future research. Soc Psychiatry Psychiatr Epidemiol. 2009; 44:887–898. [PubMed: 19277439]
11. Boscarino JA, Hoffman SN, Adams RE, Figley CR, Solhkhah R. Mental Health outcomes among vulnerable residents after Hurricane Sandy: Implications for disaster research and planning. Am J Disaster Med. 2014; 9(2):107–120. [PubMed: 25068940]

12. Adams RE, Boscarino JA. A structural equation model of perievent panic and posttraumatic stress disorder after a community disaster. J Trauma Stress. 2011; 24:61–69. [PubMed: 21351165]
13. Adams RE, Boscarino JA, Galea S. Social and psychological resources and health outcomes after the World Trade Center disaster. Soc Sci Med. 2006; 62:176–188. [PubMed: 16002196]
14. Yamashita J. A review of psychological assessments for disaster mental health studies. Psychol Trauma. 2012; 4:560–567.
15. Slobodin O, Caspi Y, Klein E, Berger BD, Hobfoll SE. Resource loss and posttraumatic responses in Bedouin members of the Israeli Defense Forces. J Trauma Stress. 2011; 24:54–60. [PubMed: 21305619]
16. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009; 114:163–173. [PubMed: 18752852]
17. Strine TW, Mokdad AH, Balluz LS, et al. Depression and anxiety in the United States: findings from the 2006 Behavioral Risk Factor Surveillance System. Psychiatr Serv. 2008; 59:1383–1390. [PubMed: 19033164]
18. Turner-Bowker DM, Bayliss MS, Ware JE Jr, Kosinski M. Usefulness of the SF-8 Health Survey for comparing the impact of migraine and other conditions. Qual Life Res. 2003; 12:1003–1012. [PubMed: 14651418]
19. Ware JE Jr, Kosinski M, Bjorner JB, et al. Applications of computerized adaptive testing (CAT) to the assessment of headache impact. Qual Life Res. 2003; 12:935–952. [PubMed: 14651413]
20. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988; 26:724–735. [PubMed: 3393032]
21. Stewart AL, Greenfield S, Hays RD, et al. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. JAMA. 1989; 262:907–913. [PubMed: 2754790]
22. Stewart, AL., Ware, JE., editors. Measuring Functioning and Well-being: The Medical Outcomes Study Approach. Durham, NC: Duke University Press; 1992.
23. Ware, JE., Kosinski, M., Turner-Bowker, DM., Gandek, B. How to Score Version 2 of the SF-12-v2 Health Survey. Boston, MA: Health Assessment Lab; 2002.
24. Ware, JE., Kosinski, M., Turner-Bowker, DM., Gandek, B. How to Score the SF-8 Health Survey. Lincoln, RI; Boston, MA: Health Assessment Lab; 2001.
25. Bradley KA, Bush KR, McDonell MB, Malone T, Fihn SD. Screening for problem drinking: comparison of CAGE and AUDIT. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. J Gen Intern Med. 1998; 13:379–388.
26. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med. 1998; 158:1789–1795. [PubMed: 9738608]
27. Freedy JR, Kilpatrick DG, Resnick HS. Natural disasters and mental health: theory, assessment, and intervention. Journal of Social Behavior and Personality. 1993; 8:49–103.
28. Sherbourne CD, Stewart AL. The MOS social support survey. Soc Sci Med. 1991; 32:705–714. [PubMed: 2035047]
29. National Center for Health Statistics. U.S. Census 2000 Population with Bridged Categories. Vol (PHS) 2003–1335. Hyattsville, Md: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2003.
30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40:373–383. [PubMed: 3558716]
31. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol. 2004; 57:1288–1294. [PubMed: 15617955]
32. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. a critical review of available methods. J Clin Epidemiol. 2003; 56:221–229. [PubMed: 12725876]

33. Austin SR, Wong YN, Uzzo RG, Beck JR, Egleston BL. Why summary comorbidity measures such as the Charlson Comorbidity Index and Elixhauser Score work. Med Care. 2013 May 23. [Epub ahead of print].

34. Stata Corporation. Stata, Version 13.1. College Station, TX: 2013.

35. Ironson G, Hayward H. Do positive psychosocial factors predict disease progression in HIV-1? A review of the evidence. Psychosom Med. 2008; 70:546–554. [PubMed: 18541905]

36. Gore-Felton C, Koopman C. Behavioral mediation of the relationship between psychosocial factors and HIV disease progression. Psychosom Med. 2008; 70:569–574. [PubMed: 18519885]

37. Lee K, Otgonsuren M, Younoszai Z, Mir HM, Younossi ZM. Association of chronic liver disease with depression: a population-based study. Psychosomatics. 2013; 54:52–59. [PubMed: 23295007]

38. Matsushita H, Ikeda F, Iwasaki Y, et al. Assessment of health-related quality of life predicts the outcome of pegylated interferon and ribavirin therapy for chronic hepatitis C. J Gastroenterol Hepatol. 2013

39. Daltro-Oliveira R, Morais-de-Jesus M, Pettersen KM, Parana R, Quarantini LC. Impact of sustained virologic response on quality of life in chronic HVC carriers. Ann Hepatol. 2013; 12:399–407. [PubMed: 23619256]

40. Evon DM, Golin CE, Fried MW, Keefe FJ. Chronic hepatitis C and antiviral treatment regimens: where can psychology contribute? J Consult Clin Psychol. 2013; 81:361–374. [PubMed: 22730952]

41. Chhatwal J, Ferrante SA, Brass C, et al. Cost-effectiveness of boceprevir in patients previously treated for chronic hepatitis C genotype 1 infection in the United States. Value Health. 2013; 16:973–986. [PubMed: 24041347]

42. Younossi ZM, Stepanova M, Henry L, et al. Minimal Impact of Sofosbuvir and Ribavirin on Health Related Quality of Life in Chronic Hepatitis C (CH-C). J Hepatol. 2014 Apr; 60(4):741–7. [PubMed: 24333184]

43. Cure S, Bianic F, Gavart S, Curtis S, Lee S, Dusheiko G. Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in previously untreated chronic hepatitis C genotype 1 patients. J Med Econ. 2014; 17:65–76. [PubMed: 24160335]

44. Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. J Hepatol. 2014; 60:530–537. [PubMed: 24269472]

Table 1

Profile of Hepatitis C Patients in the Chronic Hepatitis Cohort Study (N=4781)

Study Variable*	Total Sample (N) Percent/Mean	(95% CI)
Male	(2725) 57.0	(55.6–58.4)
Mean Age (in years)	(4781) 56.7	(56.2–57.2)
White Race	(3395) 71.0	(69.7–72.3)
Married	(2407) 50.4	(48.9–51.8)
Collage Graduate	(974) 20.4	(19.3–21.5)
Employed Full/Part-time/Occasionally	(2181) 47.9	(46.5–49.4)
Private Insurance	(2922) 61.1	(59.7–62.5)
History of IDU	(2458) 51.4	(50.0–52.8)
Ever in Drug Abuse Treatment	(1557) 32.6	(31.3–33.9)
Ever in Alcohol Abuse Treatment	(1479) 30.9	(29.6–32.3)
Current Alcohol Abuse/Dependence **	(839) 17.7	(16.6–18.8)
Ever Heavy Alc. Use, 5+ Drinks/Day	(1971) 41.2	(39.8–42.6)
Current Smoker	(1617) 33.9	(32.5–35.3)
Ever Treated for HCV	(2268) 47.4	(46.0–48.9)
Stopped HCV Meds Past 12 Months	(711) 14.9	(13.9–15.9)
Currently on HCV Meds Past 4 Weeks	(227) 4.7	(4.2–5.4)
Liver Transplant	(285) 6.0	(5.3–6.7)
SVR 12 Weeks	(705) 14.8	(13.8–15.8)
HCV Genotype 1 ***	(2486) 84.2	(82.8–85.5)
Decompensated or ESLD	(258) 5.4	(4.8–6.1)
High Charlson Disease Score	(694) 14.5	(13.6–15.5)
PHQ-8 Depression Positive	(1409) 29.7	(28.4–31.0)
SF-8 Poor Physical Health	(1088) 24.6	(23.3–25.9)

* IDU = injection drug use; HCV = hepatitis C virus; SVR = sustained virologic response; ESLD = end stage liver disease; PHQ-8 = Patient Health Questionnaire-8; SF-8 = Short From-8.

** Based on the AUDIT-C Scale.

*** Genotype based on n = 2,938, due to missing data.

Table 2

PHQ-8 Depression Results by Key Study Variables (N=4,742-4,451)

Study Variable*	No Depression (N) Percent	Depression (N) Percent	Depression: Bivariate OR (95% CI)	Depression: Multivariate** OR (95% CI)
Gender				
Female	(1354) 66.4	(684) 33.6	1.00	1.00
Male	(1979) 73.2	(725) 26.8	0.73 (0.64–0.82) ¶	0.70 (0.59–0.82) ¶
Age				
20–44	(303) 61.0	(194) 39.0	2.41 (1.86–3.12) ¶	2.27 (1.55–3.31) ¶
45–54	(689) 64.0	(388) 36.0	2.12 (1.69–2.65) ¶	2.61 (1.91–3.56) ¶
55–64	(1809) 72.5	(686) 27.5	1.43 (1.16–1.75) ǂ	2.02 (1.53–2.67) ¶
65+	(530) 79.0	(141) 21.0	1.00	1.00
Race				
White	(2331) 69.0	(1047) 31.0	1.00	1.00
Black	(694) 73.4	(251) 26.6	0.81 (0.69–0.95) ǂ	0.60 (0.47–0.76) ¶
Asian/PI	(176) 78.9	(47) 21.1	0.60 (0.43–0.83) ǂ	0.75 (0.48–1.17)
Other/Unknown	(132) 67.3	(64) 32.7	1.08 (0.79–1.47)	0.83 (0.57–1.21)
Hispanic				
No	(3182) 70.3	(1342) 29.7	1.00	--
Yes	(151) 69.3	(67) 30.7	1.05 (0.78–1.41)	--
Born in USA				
No	(254) 76.7	(77) 23.3	1.00	--
Yes	(3079) 69.8	(1332) 30.2	1.43(1.10–1.86) ǂ	--
Married				
No	(1516) 64.5	(833) 35.5	1.00	--
Yes	(1817) 75.9	(576) 24.1	0.58 (0.51–0.65) ¶	--
Income				
Less than $30K	(565) 64.4	(312) 35.6	1.79 (1.49–2.14) ¶	--
$30–49K	(1536) 68.2	(717) 31.8	1.51(1.31–1.75) ¶	--
$50K or more	(1185) 76.4	(366) 23.6	1.00	--
Education				
Less than HS	(303) 58.3	(217) 41.7	2.79 (2.21–3.52) ¶	1.81 (1.36–2.41) ¶
HS/GED	(794) 65.5	(419) 34.5	2.06 (1.69–2.50) ¶	1.57 (1.25–1.98) ¶
Some College	(1140) 73.5	(412) 26.5	1.41 (1.16–1.71) ¶	1.19 (0.95–1.49)
College Grad or higher	(775) 79.6	(199) 20.4	1.00	1.00
Employment				

Study Variable*	No Depression (N) Percent	Depression (N) Percent	Depression: Bivariate OR (95% CI)	Depression: Multivariate** OR (95% CI)
Full-time/part-time/occasionally	(1787) 82.2	(388) 17.8	0.33 (0.29–0.38) ¶	0.36 (0.30–0.44) ¶
Unemployed/retired/disabled	(1419) 60.3	(934) 39.7	1.00	1.00
Health Insurance				
Private	(2213) 76.2	(690) 23.8	1.00	1.00
Medicaid	(225) 47.2	(252) 52.8	3.59 (2.94–4.38) ¶	1.57 (1.19–2.06) ǂ
Medicare	(790) 67.1	(387) 32.9	1.57 (1.35_1.82) ¶	1.17 (0.93–1.47)
None reported	(105) 56.8	(80) 43.2	2.44 (1.81–3.31) ¶	1.47 (1.00–2.17) †
History of IDU				
No	(1673) 72.9	(622) 27.1	1.00	--
Yes	(1660) 67.8	(787) 32.2	1.28 (1.23–1.45) ¶	--
Ever Alcohol Treatment				
No	(2397) 73.2	(878) 26.8	1.00	--
Yes	(936) 63.8	(531) 36.2	1.55 (1.36–1.77) ¶	--
Ever Drug Treatment				
No	(2378) 74.5	(815) 25.5	1.00	1.00
Yes	(955) 61.7	(594) 38.3	1.82 (1.59–2.07) ¶	1.51 (1.27–1.80) ¶
Current Smoker				
No	(2371) 75.6	(764) 24.4	1.00	1.00
Yes	(962) 59.9	(645) 40.1	2.08 (1.83–2.37) ¶	1.26 (1.06–1.50) †
Current Alcohol Abuse/Depend.				
No	(2764) 71.2	(1119) 28.8	1.00	--
Yes	(555) 66.5	(280) 33.5	1.25 (1.06–1.46) ǂ	--
Life Stressors - past year				
Low	(2101) 77.6	(608) 22.4	1.00	1.00
Moderate	(872) 66.6	(438) 33.4	1.74 (1.50–2.01) ¶	1.48 (1.24–1.77) ¶
High	(360) 49.8	(363) 50.2	3.48 (2.94–4.14) ¶	2.44 (1.96–3.03) ¶
Social Support - past year				
Low	(600) 55.4	(483) 44.6	3.34 (2.82–3.96) ¶	2.78 (2.27–3.40) ¶
Moderate	(1124) 68.3	(521) 31.7	1.92 (1.64–2.25) ¶	1.68 (1.39–2.02) ¶
High	(1403) 80.6	(338) 19.4	1.00	1.00
HCV Treatment Naive				
No	(1613) 71.5	(643) 28.5	1.00	--
Yes	(1720) 69.2	(766) 30.8	1.12(0.99–1.27)	--
Currently on HCV meds past 4 wks				

Study Variable*	No Depression (N) Percent	Depression (N) Percent	Depression: Bivariate OR (95% CI)	Depression: Multivariate** OR (95% CI)
No	(3190) 70.6	(1326) 29.4	1.00	1.00
Yes	(143) 63.3	(83) 36.7	1.40 (1.06–1.84) †	1.58 (1.11–2.25) †
Stopped HCV meds past 12 mos.				
No	(2834) 70.2	(1201) 29.8	1.00	1.00
Yes	(499) 70.6	(208) 29.4	0.98 (0.83–1.17)	0.82 (0.65–1.04)
Ever Visited Hepatologist				
No	(574) 68.9	(259) 31.1	1.00	--
Yes	(2759) 70.6	(1150) 29.4	0.92 (0.79–1.09)	--
Ever Liver Transplant				
No	(3137) 70.4	(1322) 29.6	1.00	--
Yes	(196) 69.3	(87) 30.7	1.05 (0.81–1.37)	--
Charlson Score				
No Disease Score	(1922) 73.3	(699) 26.7	1.00	1.00
Low Score	(700) 68.0	(330) 32.0	1.30 (1.11–1.52) ‡	1.30 (1.06–1.58) †
Moderate Score	(286) 70.4	(120) 29.6	1.15 (0.92–1.45)	1.25 (0.94–1.67)
High Score	(425) 62.0	(260) 38.0	1.68 (1.41–2.01) ¶	1.58 (1.24–2.00) ¶
Decompensated or ESLD				
No	(3164) 70.5	(1321) 29.5	1.00	--
Yes	(169) 65.8	(88) 34.2	1.24 (0.96–1.63)	--
Ever used Ribavirin				
No	(1853) 69.2	(825) 30.8	1.00	--
Yes	(1480) 71.7	(584) 28.3	0.89 (0.78–1.01)	--
Ever used Pegylated interferon-alfa				
No	(1999) 69.6	(873) 30.4	1.00	1.00
Yes	(1334) 71.3	(536) 28.7	0.92 (0.81–1.05)	1.21 (1.01–1.45) †
Sustained 12 week Viral Response				
No	(2786) 68.9	(1255) 31.1	1.00	1.00
Yes	(547) 78.0	(154) 22.0	0.63 (0.52–0.76) ¶	0.72 (0.56–0.92) ‡

*IDU = injection drug use; HCV = hepatitis C virus; SVR = sustained virologic response; ESLD = end stage liver disease; PHQ-8 = Patient Health Questionnaire-8; Current alcohol abuse/dependence based on the AUDIT-C Scale; Depression defined as present for PHQ-8 score ≥ 10.

**In multivariate analyses, forward stepwise regression used, with $p < 0.10$ for inclusion, $p < 0.10$ exclusion, with only variables $p < 0.20$ included from bivariate analyses. Study site (KPNW, KPHI, HFHS, GHS) was forced entered at first step for multivariate analyses, otherwise only the variables shown in the multivariate column were included in the final model.

†$p < 0.05$;

‡$p < 0.01$;

¶$p < 0.001$.

Table 3

SF-8 Physical Health Results by Key Study Variables (N=4,427-4,183)

Study Variable*	Not Poor Health (N) Percent	Poor Health (N) Percent	Poor Health: Bivariate OR (95% CI)	Poor Health: Multivariate** OR (95% CI)
Gender				
Female	(1390) 73.7	(495) 26.3	1.00	1.00
Male	(1949) 76.7	(593) 23.3	0.85 (0.74–0.98)†	0.81 (0.68–0.97)†
Age				
20–44	(390) 82.8	(81) 17.2	0.63 (0.47–0.85)‡	1.01 (0.67–1.54)
45–54	(755) 74.8	(255) 25.2	1.02 (0.81–1.29)	2.09 (1.53–2.85)¶
55–64	(1719) 74.3	(596) 25.7	1.05 (0.86–1.29)	2.12 (1.61–2.79)¶
65+	(473) 75.2	(156) 24.8	1.00	1.00
Race				
White	(2375) 75.0	(791) 25.0	1.00	1.00
Black	(661) 75.0	(220) 25.0	0.99 (0.84–1.19)	0.61 (0.49–0.83)‡
Asian/PI	(176) 85.0	(31) 15.0	0.53 (0.36–0.78)‡	0.56 (0.33–0.93)†
Other/Unknown	(127) 73.4	(46) 26.6	1.09 (0.77–1.54)	0.95 (0.63–1.45)
Hispanic				
No	(3190) 75.5	(1033) 24.5	1.00	--
Yes	(149) 73.0	(55) 27.0	1.14 (0.83–1.57)	--
Born in USA				
No	(248) 80.0	(62) 20.0	1.00	--
Yes	(3091) 75.1	(1026) 24.9	1.33 (0.99–1.77)	--
Married				
No	(1576) 72.5	(598) 27.5	1.00	--
Yes	(1763) 78.3	(490) 21.7	0.73 (0.64–0.84)¶	--
Income				
Less than $30K	(558) 70.4	(235) 29.6	1.80 (1.47–2.20)¶	1.32 (1.01–1.74)†
$30–49K	(1545) 73.2	(567) 26.8	1.57 (1.34–1.85)¶	1.27 (1.04–1.57)†
$50K or more	(1189) 81.0	(278) 19.0	1.00	1.00
Education				
Less than HS	(304) 64.7	(166) 35.3	2.27 (1.77–2.91)¶	1.54 (1.13–2.08)‡
HS/GED	(858) 74.2	(298) 25.8	1.44 (1.17–1.78)‡	1.17 (0.91–1.50)
Some College	(1142) 77.7	(327) 22.3	1.19 (0.97–1.46)	1.02 (0.80–1.29)
College Grad or higher	(743) 80.6	(179) 19.4	1.00	1.00
Employment				

Study Variable*	Not Poor Health (N) Percent	Poor Health (N) Percent	Poor Health: Bivariate OR (95% CI)	Poor Health: Multivariate** OR (95% CI)
Full-time/part-time/occasionally	(1858) 89.5	(218) 10.5	0.20 (0.17–0.24)¶	0.25 (0.20–0.31)¶
Unemployed/retired/disabled	(1367) 63.2	(797) 36.8	1.00	1.00
Health Insurance				
Private	(2239) 82.2	(484) 17.8	1.00	1.00
Medicaid	(282) 65.1	(151) 34.9	2.48 (1.99–3.09¶	1.56 (1.15–2.09)‡
Medicare	(699) 63.7	(398) 36.3	2.63 (2.25–3.08¶	1.48 (1.17–1.86)‡
None reported	(119) 68.4	(55) 31.6	2.14 (1.53–2.99)¶	1.72 (1.13–2.62)†
History of IDU				
No	(1549) 72.2	(596) 27.8	1.00	1.00
Yes	(1790) 78.4	(492) 21.6	0.71 (0.62–0.82)¶	0.63 (0.51–0.76)¶
Ever Alcohol treatment				
No	(2308) 75.5	(748) 24.5	1.00	--
Yes	(1031) 75.2	(340) 24.8	1.02 (0.88–1.18)	--
Ever Drug treatment				
No	(2266) 75.5	(736) 24.5	1.00	1.00
Yes	(1073) 75.3	(352) 24.7	1.01 (0.87–1.17)	1.20 (0.97–1.48)
Current Smoker				
No	(2268) 77.2	(670) 22.8	1.00	--
Yes	(1071) 71.9	(418) 28.1	1.32 (1.15–1.52)¶	--
Current Alcohol Abuse/Depend.				
No	(2718) 75.1	(901) 24.9	1.00	--
Yes	(607) 77.1	(180) 22.9	0.90 (0.75–1.07)	--
Life Stressors - past year				
Low	(2013) 79.0	(534) 21.0	1.00	1.00
Moderate	(903) 74.1	(316) 25.9	1.32 (1.12–1.55)‡	1.22 (1.00–1.48)†
High	(423) 64.0	(238) 36.0	2.12 (1.76–2.55)¶	1.64 (1.30–2.08)¶
Social Support - past year				
Low	(684) 68.5	(315) 31.5	1.85 (1.55–2.22)¶	1.40 (1.12–1.75)‡
Moderate	(1150) 74.6	(391) 25.4	1.37 (1.16–1.62)¶	1.26 (1.03–1.54)†
High	(1316) 80.1	(327) 19.9	1.00	1.00
HCV Treatment Naive				
No	(1611) 76.4	(498) 23.6	1.00	--
Yes	(1728) 74.5	(590) 25.5	1.11 (0.96–1.27)	--
Currently on HCV meds past 4 wks				

Study Variable*	Not Poor Health (N) Percent	Poor Health (N) Percent	Poor Health: Bivariate OR (95% CI)	Poor Health: Multivariate** OR (95% CI)
No	(3195) 75.7	(1024) 24.3	1.00	--
Yes	(144) 69.2	(64) 30.8	1.39 (1.02–1.88)†	--
Stopped HCV meds - past 12 mos.				
No	(2856) 75.8	(912) 24.2	1.00	--
Yes	(483) 73.3	(176) 26.7	1.14 (0.95–1.38)	--
Ever Visited Hepatologist				
No	(545) 70.4	(229) 29.6	1.00	1.00
Yes	(2794) 76.5	(859) 23.5	0.73 (0.62–0.87)¶	0.82 (0.66–1.02)
Ever Liver Transplant				
No	(3158) 75.9	(1001) 24.1	1.00	--
Yes	(181) 67.5	(87) 32.5	1.52 (1.16–1.98)‡	--
Charlson Score				
No Disease Score	(2005) 81.8	(445) 18.2	1.00	1.00
Low Score	(682) 71.6	(270) 28.4	1.78 (1.50–2.12)¶	1.64 (1.32–2.03)¶
Moderate Score	(269) 70.1	(115) 29.9	1.93 (1.51–2.45)¶	1.65 (1.23–2.22)‡
High Score	(383) 59.8	(258) 40.2	3.04 (2.51–3.66)¶	2.12 (1.67–2.74)¶
Decompensated or ESLD				
No	(3174) 75.9	(1007) 24.1	1.00	--
Yes	(165) 67.1	(81) 32.9	1.55 (1.18–2.04)‡	--
Ever used Ribavirin				
No	(1849) 74.0	(649) 26.0	1.00	--
Yes	(1490) 77.2	(439) 22.8	0.84 (0.73–0.97)†	--
Ever used Pegylated interferon-alfa				
No	(1971) 73.7	(705) 26.3	1.00	--
Yes	(1368) (78.1)	(383) 21.9	0.78 (0.68–0.90)‡	--
Sustained 12 week Viral Response				
No	(2812) 74.5	(964) 25.5	1.00	--
Yes	(527) 81.0	(124) 19.0	0.69 (0.56–0.85)¶	--

*IDU = injection drug use; HCV = hepatitis C virus; SVR = sustained virologic response; ESLD = end stage liver disease; SF-8 = Short From-8; Current alcohol abuse/dependence based on the AUDIT-C Scale; Low SF-8 Physical Health Score defined as the lowest quartile range.

**In multivariate analyses, forward stepwise regression used, with $p < 0.10$ for inclusion, $p < 0.10$ exclusion, with only variables $p < 0.20$ included from bivariate analyses. Study site (KPNW, KPHI, HFHS, GHS) was forced entered at first step for multivariate analyses, otherwise only the variables shown in the multivariate column were included in the final model.

†$p < 0.05$;

‡$p < 0.01$;

¶ $p < 0.001$.