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ORIGINAL RESEARCH—CLINICAL

Comparing the Risk of Poor Outcomes Among Hepatitis C–Infected, Cured, and Never-Infected Controls

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BACKGROUND AND AIMS: Studies show decreased rates of poor outcomes after hepatitis C virus (HCV) cure. However, there are no data comparing risk of poor outcomes to that of HCV never infected; results that could have implications for those who may not need ongoing specialty follow-up after cure. **METHODS:** Retrospective cohort study conducted among Kaiser Permanente Northern California adults ages 18 and up between 2002 and 2019. Three cohorts were identified: 1) chronic HCV, 2) HCV cured, and 3) every chronic HCV and HCV-cured individual was matched by age, sex and race-ethnicity to 3 HCV negative controls. Outcomes of interest were cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC) and all-cause mortality. A low-risk group of HCV cured individuals without significant liver disease and/or concomitant liver disease cofactor(s) were identified. **RESULTS:** We identified 21,184 chronic HCV, 11,950 HCV cure, and 99,402 control individuals. Five-year cumulative incidence of cirrhosis, decompensated cirrhosis, HCC and all-cause mortality was 10% vs 3.6% vs 0.8%, 12% vs 2.6% vs 0.6%, 3.9% vs 1.6% vs 0.07%, and 14% vs 2.8% vs 2.2% for chronic HCV, HCV cure, and control individuals, respectively (log-rank $P < .01$ for all). Compared to controls, HCV cured low-risk individuals had numerically similar 5-year cumulative incidence of cirrhosis, decompensated cirrhosis, HCC and all-cause mortality (1.2% vs 0.8%, $P < .01$; 0.9% vs 0.6%, $P < .01$; 0.5% vs 0.1%, $P < .01$; 1.7% vs 2.2%, $P < .01$). **CONCLUSION:** HCV cure provides significant health benefits but does not universally return risk of poor outcomes to that of the general population. A simple stratification at the time of HCV cure could identify low-risk individuals who can potentially be discharged from specialty clinics/HCC surveillance.

Keywords: Hepatitis C Cure; Cirrhosis; Decompensated Cirrhosis; Hepatocellular Carcinoma; Population Management; Inclusion

Introduction

The US prevalence of chronic infection with the hepatitis C virus (HCV) is estimated to be 2,266,700 individuals or 0.93% of the total adult population.[1] Chronic infection with HCV may lead to the development of hepatic fibrosis, which can progress to cirrhosis, increased risk of decompensated cirrhosis, development of hepatocellular carcinoma (HCC) and increased all-cause mortality.[2] A meta-analysis found that chronic HCV-infected individuals with advanced hepatic fibrosis had an overall annual risk of 2.9% to experience liver failure, 3.2% to develop HCC and 2.7% to die of liver-related causes.[3] It is expected that there will be an increase in the incidence of HCV-induced cirrhosis and its clinical complications in Western countries, and it is estimated that almost half of the US population with chronic HCV infection will have cirrhosis by 2030.[4,5]

HCV cure is defined as undetectable HCV viral load 12 weeks after cessation of treatment. Antiviral therapy against HCV has been available since the early 1990s, and while HCV cure rates were disappointing with the early regimens,[6] the efficacy has improved significantly with the development of direct-acting antiviral drugs.[7] Several studies have shown that achieving HCV cure is associated with reduced risk of developing cirrhosis, decompensated cirrhosis, HCC and all-cause mortality compared to ongoing HCV infection.[8–16] However, we assume that the risk of these poor outcomes does not reduce entirely to that of an HCV never-infected general population and likely those with more advanced liver disease before HCV treatment and/or significant additional liver diseases like nonalcoholic fatty liver disease (NAFLD), chronic hepatitis B virus (HBV) infection and alcohol-associated liver disease remain at risk.[15,16] As a result, the American Association for the Study of Liver Diseases recommends ongoing HCC surveillance in HCV-cured patients that had cirrhosis before HCV treatment.[17] Unfortunately, there are currently no data that examine if achievement of HCV cure improves risk of poor outcomes back to the general, HCV never-infected population. This information is critical to understanding who after HCV cure would need ongoing follow-up and who can safely be discharged from liver-specific specialty clinics and HCC surveillance protocols.

Abbreviations used in this paper: **FIB-4, Fibrosis-4; HBV, Hepatitis B virus; HCV, Hepatitis C virus; KPNC, Kaiser Permanente Northern California; NAFLD, Nonalcoholic fatty liver disease.**

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In this study of all HCV-infected Kaiser Permanente Northern California (KPNC) adults, a demographically representative cohort of insured Northern Californians, we investigated the impact of HCV cure on risk of cirrhosis, decompensated cirrhosis, HCC and all-cause mortality and whether HCV cured individuals' risk of poor outcomes approaches that of HCV never infected controls. We also investigated if HCV cured "low-risk" individuals without significant baseline liver fibrosis and/or concomitant liver disease cofactor(s) would have a risk of poor outcomes that approaches that of controls.

Material and Methods

Cohorts

This retrospective cohort study included all chronic HCV infected adult (≥18 years of age) KPNC members from January 1, 2002, through June 1, 2019. KPNC is an integrated healthcare organization providing comprehensive medical services to more than 30% of insured Californians and its members are representative of insured Northern Californians.[18]

Chronic HCV. We defined members as having chronic HCV infection if they had a positive hepatitis C antibody test at the study period and at least 1 positive qualitative HCV ribonucleic acid (RNA) or a detectable quantitative HCV RNA test. Identified individuals who no longer had detectable HCV RNA greater than 6 months after HCV RNA detectability and without HCV treatment were excluded as they were likely individuals who spontaneously cleared infection. Entry into the chronic HCV cohort was defined as the time when HCV antibody was positive and baseline variables were collected at time of cohort entry ±3 months.

HCV cure. Among identified chronic HCV infected members, we also monitored for achievement of HCV cure, defined as treatment of HCV followed by sustained undetectable HCV RNA at least 12 weeks after HCV treatment completion. Entry into the HCV-cured cohort was defined as the first time point after HCV treatment completion where HCV RNA remained undetectable and baseline variables were collected at time of cohort entry ±3 months. HCV treatment was identified by referencing pharmacy data for anti-HCV medications including injectables during interferon era and all direct-acting antivirals.

Control. All individuals identified in chronic HCV and HCV-cured cohorts were matched to 3 HCV never infected adult (≥18 years of age) controls on age in years, sex and race/ethnicity. An individual with chronic HCV who is later cured of HCV can contribute person-time to both chronic HCV and HCV-cured cohorts and can be matched to 6 controls, 3 at the time of entry into the chronic HCV cohort and 3 at the time of entry into the HCV-cured cohort. Individuals of each of the 3 cohorts (chronic HCV, HCV cure, and control) were followed until reaching outcome of interest, membership end or study end, whichever occurred earliest.

Data Sources

Utilizing the KPNC electronic medical record including laboratory and pharmacy records, data were obtained on individual demographics, body mass index (BMI), alcohol disorder, substance use disorder, tobacco status, HIV status, chronic hepatitis B status, laboratory results, diabetes (based on diagnosis codes and/or prescription for antidiabetic medication), statin use, antiplatelet use (including aspirin and clopidogrel), and ace-inhibitor use.

Clinical Outcomes

Outcomes of interest included development of cirrhosis, decompensated cirrhosis, HCC and all-cause mortality. Cirrhosis was defined via a previously validated approach using inpatient and outpatient diagnosis codes[19] and/or via fibrosis-4 (FIB-4) score ≥3.25 in the absence of a diagnosis of immune thrombocytopenic purpura. Decompensated cirrhosis was defined via a previously validated approach using inpatient and outpatient diagnosis codes and/or prescription data for treatments of ascites (furosemide and spironolactone prescriptions), of hepatic encephalopathy (lactulose and/or rifaximin) and of esophageal varices (nonselective beta blockers of nadolol, propranolol and/or carvedilol). Development of HCC was ascertained by referencing the curated KPNC Cancer Registry, a contributor to the Surveillance, Epidemiology, and End Results program. All-cause mortality data were obtained from California death certificates and Social Security Administration datasets. Last date of outcome ascertainment was June 1, 2021.

HCV Cure Low-Risk and High-Risk Stratification

The HCV-cured cohort was stratified into a low-risk and high-risk group. High-risk was defined *a priori* as individuals with evidence of either significant baseline liver disease at the time of HCV-cured cohort entry (ie, albumin <3.5 g/dL, platelets <150 $10^3/\mu$L or total bilirubin >1.0 mg/dL) or presence of liver disease cofactor of NAFLD (defined as presence of diabetes, BMI ≥30 kg/m^2 or aspartate aminotransferase (AST) >40 U/L), alcohol-associated liver disease (defined as alcohol disorder) or chronic HBV. We defined NAFLD as such given the ease of clinical use and that patients with diabetes and obesity (BMI ≥30 kg/m^2) have a >90% prevalence of the condition.[20–23] We further examined the patients that were included in the high-risk category for NAFLD cofactor as we defined and calculated their Dallas Steatosis Index (DSI),[24] a risk equation with excellent precision of identifying underly NAFLD, and all patients were found to have a DSI score consistent with NAFLD diagnosis.

Statistical Analyses

Descriptive analyses were performed using cross-tabulations with chi-square tests. Kaplan-Meier plots for cumulative incidence of outcome by cohort were performed with log-rank testing comparing 5-year cumulative risk. Each of the 3 outcomes were also modeled using Cox proportional hazards regression to examine benefit of HCV cure in relation to chronic HCV and controls while controlling for baseline factors. Within the HCV cure group, we examined predictors of outcomes while controlling for nonmatched variables using cox-proportional hazard models. Exclusions were applied for individual outcomes as follows: for cirrhosis, individuals who had cirrhosis within 6 months of cohort entry were excluded; for decompensated cirrhosis, individuals who had cirrhosis or decompensated cirrhosis within 6 months of cohort entry were excluded; and for HCC, individuals with HCC within 6 months of cohort entry were excluded.

Statistical analyses were performed using SAS® version 9.4. There is no relevant reporting guidelines/checklist to disclose.

This study was approved by the KPNC Institutional Review Board.

Results

Study Population

A total of 21,184 chronic HCV, 11,950 HCV-cured, and 99,402 controls were identified. Table 1 shows the baseline characteristics of each cohort. Of the 11,950 HCV-cured individuals, 7540 (63%) were classified as high risk and 4410 (37%) as low risk. Table 2 shows the baseline characteristics of HCV cure, HCV-cured high risk, and HCV-cured low risk.

Cirrhosis

Development of cirrhosis was far more common among chronic HCV individuals (n = 3890 or 18%) than

Table 1. Baseline Characteristics of Chronic HCV, HCV-cured, and Controls

Continuous: median (IQR) Categorical: n (%)	Chronic HCV (N = 21,184)	HCV cure (N = 11,950)	Controls (N = 99,402)
Age (y)	54 (47–60)	59 (52–64)	54 (45–62)
Female	8022 (38)	4759 (40)	38,343 (39)
Race/Ethnicity			
White	10,957 (52)	6459 (54)	52,248 (53)
Hispanic	3628 (17)	1953 (16)	16,743 (17)
African American	3326 (16)	1709 (14)	15,105 (15)
Asian	1370 (7)	922 (7)	6876 (7)
Other/Multiple	1903 (9)	907 (8)	8430 (8)
BMI (kg/m^2)	27 (24–31)	28 (24–32)	29 (25–33)
Alcohol use disorder	1829 (9)	446 (4)	1216 (1)
Substance use disorder	2241 (11)	771 (7)	830 (1)
Tobacco status			
Current	6561 (31)	2369 (20)	5783 (6)
Former	5725 (27)	5176 (43)	14,546 (15)
Never	5673 (27)	3728 (31)	32,234 (32)
Unknown	3225 (15)	677 (6)	46,839 (47)
HIV positive	655 (3)	411 (3)	1140 (1)
Hepatitis B status			
Nonexposed/untested	14,886 (70)	8271 (70)	95,238 (96)
Isolated hepatitis B core antibody+	2302 (11)	1210 (10)	485 (1)
Exposed with natural immunity	3910 (19)	2415 (20)	3154 (3)
Chronic hepatitis B	86 (0.4)	54 (1)	525 (1)
HCV genotype			
1	12,610 (60)	7925 (66)	
3	2037 (10)	1260 (11)	
Other	6537 (31)	2765 (23)	
Cirrhosis	1049 (5)	1947 (16)	655 (1)
MELD	10 (7–14)	8 (7–10)	10 (7–14)
Childs-Pugh B/C	474 (45)	357 (18)	90 (14)
Transient elastography (kPa)	7 (5–10) (n = 1471)	7 (5–11) (n = 3042)	6 (4–12) (n = 17)
Fibrosis-4 score	1.58 (1.04–2.72) (n = 17,356)	1.52 (1.06–2.31) (n = 11,255)	1.08 (0.78–1.58) (n = 12,340)
Total bilirubin (mg/dL)	0.7 (0.5–0.9) (n = 17,160)	0.6 (0.5–0.8) (n = 11,477)	0.6 (0.4–0.8) (n = 9853)
Aspartate transaminase (U/L)	45 (30–76) (n = 18,630)	22 (18–30) (n = 11,458)	22 (17–29) (n = 15,072)
Alanine transaminase (U/L)	54 (33–94) (n = 20,693)	19 (14–27) (n = 11,862)	21 (15–31) (n = 36,077)
Albumin (g/dL)	4.2 (3.9–4.4) (n = 13,752)	4.2 (4.0–4.4) (n = 10,588)	4.2 (3.8–4.4) (n = 6467)
Platelets (10^3/μL)	211 (164–261) (n = 19,502)	203 (156–252) (n = 11,654)	241 (202–285) (n = 38,285)
INR	1.0 (1.0–1.1) (n = 15,019)	1.0 (1.0–1.1) (n = 11,011)	1.0 (1.0–1.2) (n = 7330)
Estimated glomerular filtration rate (mL/min)	95 (82–104) (n = 21,184)	91 (78–100) (n = 11,950)	97 (87–105) (n = 99,402)
Alpha-fetoprotein (ng/mL)	5 (3–8) (n = 9836)	4 (3–7) (n = 8033)	3 (2–5) (n = 708)
Diabetes	3176 (15)	2172 (18)	14,082 (14)
Statin	2890 (14)	2121 (18)	22,046 (22)
Aspirin	2188 (10)	1358 (11)	6261 (6)
Clopidogrel	302 (1)	194 (2)	1127 (1)
ACE-inhibitor	4412 (21)	2474 (21)	14,208 (14)

ACE, angiotensin-converting enzyme; BMI, body mass index; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; kPa, kilopascals; MELD, model for end-stage liver disease.

Table 2. Baseline Characteristics of HCV-Cured, HCV-Cured High-Risk, and HCV-Cured Low-Risk

Continuous: median (IQR) Categorical: n (%)	HCV cure (N = 11,950)	HCV cure high-risk (N = 7540)	HCV cure low-risk (N = 4410)
Age (y)	59 (52–64)	59 (52–64)	59 (51–64)
Female	4759 (40)	2804 (37)	1955 (44)
Race/Ethnicity			
White	6459 (54)	3872 (51)	2587 (59)
Hispanic	1953 (16)	1415 (19)	538 (12)
African American	1709 (14)	1185 (16)	524 (12)
Asian	922 (7)	507 (7)	415 (9)
Other/Multiple	907 (8)	561 (7)	346 (8)
BMI (kg/m^2)	28 (24–32)	30 (26–34)	26 (23–28)
Alcohol use disorder	446 (4)	446 (6)	0 (0)
Substance use disorder	771 (7)	540 (7)	231 (5)
Tobacco status			
Current	2369 (20)	1438 (19)	931 (21)
Former	5176 (43)	3355 (44)	1821 (41)
Never	3728 (31)	2328 (31)	1400 (32)
Unknown	677 (6)	419 (6)	258 (6)
HIV positive	411 (3)	248 (3)	163 (4)
Hepatitis B status			
Nonexposed/untested	8271 (70)	5161 (68)	3110 (71)
Isolated hepatitis B core antibody+	1210 (10)	813 (11)	397 (9)
Exposed with natural immunity	2415 (20)	1512 (20)	903 (20)
Chronic hepatitis B	54 (1)	54 (1)	0 (0)
HCV genotype			
1	7925 (66)	4960 (70)	2965 (71)
3	1260 (11)	821 (12)	439 (11)
Other	2765 (23)	1759 (18)	1006 (18)
Cirrhosis	1947 (16)	1721 (23)	226 (5)
MELD	8 (7–10)	8 (7–10)	7 (6–8)
Childs-Pugh B/C	357 (18)	382 (5)	10 (0)
Transient elastography (kPa)	7 (5–11) (n = 3042)	8 (6–13) (n = 1729)	6 (5–8) (n = 1313)
Total bilirubin (mg/dL)	0.6 (0.5–0.8) (n = 11,477)	0.7 (0.5–1.0) (n = 7302)	0.5 (0.4–0.7) (n = 4175)
Aspartate transaminase (U/L)	22 (18–30) (n = 11,458)	24 (19–36) (n = 7278)	20 (17–24) (n = 4180)
Alanine transaminase (U/L)	19 (14–27) (n = 11,862)	21 (15–30) (n = 7510)	16 (12–21) (n = 4352)
Albumin (g/dL)	4.2 (4.0–4.4) (n = 10,588)	4.1 (3.9–4.4) (n = 6781)	4.3 (4.1–4.4) (n = 3807)
Platelets (10^3/μL)	203 (156–252) (n = 11,654)	183 (131–239) (n = 7432)	226 (192–266) (n = 4222)
INR	1.0 (1.0–1.1) (n = 11,011)	1.0 (1.0–1.1) (n = 7540)	1.0 (1.0–1.0) (n = 3958)
Estimated glomerular filtration rate (mL/min)	91 (78–100) (n = 11,950)	91.4 (76.9–100.6) (n = 7540)	90.8 (78.8–100.0) (n = 4410)
Alpha-fetoprotein (ng/mL)	4 (3–7) (n = 8033)	4.7 (2.9–8.4) (n = 5313)	3.4 (2.4–5.4) (n = 2720)
Diabetes	2172 (18)	2172 (29)	0 (0)
Statin	2121 (18)	1648 (22)	473 (11)
Aspirin	1358 (11)	1029 (14)	329 (7)
Clopidogrel	194 (2)	147 (2)	47 (1)
ACE-inhibitor	2474 (21)	1886 (25)	588 (13)

ACE, angiotensin-converting enzyme; BMI, body mass index; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; kPa, kilopascals; MELD, model for end-stage liver disease.

among HCV-cured individuals (n = 489 or 4%) but remained more common among HCV-cured individuals than among controls (n = 1139 or 1%) ($P < .01$) (Table 3). Among HCV-cured individuals, we identified those who may have had advanced fibrosis at baseline of their HCV treatment with either a FIB-4 score > 1.3 (n = 6899) or a transient elastography consistent with stage 3 fibrosis (median kPa between 9 and 14) (n = 560). Of the FIB-4 score >1.3 individuals, 231 went on to develop cirrhosis after HCV cure and of the transient elastography stage 3 fibrosis, 11 went on to develop cirrhosis after HCV cure.

In models controlling for other baseline factors, risk of cirrhosis was 240% higher among chronic HCV (hazard ratio (HR): 3.4, 95% confidence interval (CI): 3.0–3.9, $P < .01$) compared to controls and remained 70% higher among HCV-cured individuals compared to controls (HR: 1.7, 95% CI: 1.5–2.1, $P < .01$) (Table 4).

Table 3. Outcomes Among Chronic HCV, HCV-Cured, Controls, HCV-Cured High-Risk, and HCV-Cured Low-Risk

n (%)	Chronic HCV (N = 21,184)	HCV cure (N = 11,950)	Controls (N = 99,402)	*P* value
Cirrhosis[a]	3890 (18)	489 (4)	1139 (1)	<.01
Decompensated cirrhosis[b]	2285 (11)	332 (3)	913 (1)	<.01
Hepatocellular carcinoma[c]	814 (4)	138 (1)	98 (0.1)	<.01
All-cause mortality	3390 (16)	468 (4)	3515 (4)	<.01

n (%)	HCV-cured (N = 11,950)	HCV-cured high-risk (N = 7540)	HCV-cured low-risk (N = 4410)	*P* value
Cirrhosis[a]	489 (4)	448 (6)	41 (1)	<.01
Decompensated cirrhosis[b]	332 (3)	325 (4)	7 (0.2)	<.01
Hepatocellular carcinoma[c]	138 (1)	127 (2)	11 (0.2)	<.01
All-cause mortality	468 (4)	437 (6)	31 (0.7)	<.01

P values are for comparisons of all 3 cohorts in upper half and comparison of HCV, cure high-risk vs low-risk in the lower half.
HCV, hepatitis C virus.
[a]Excludes baseline cirrhosis.
[b]Excludes baseline decompensated cirrhosis.
[c]Excludes baseline hepatocellular carcinoma.

Development of cirrhosis was far more common among HCV-cured high-risk individuals (n = 448 or 6%) than among HCV-cured low-risk individuals (n = 41 or 1%) ($P <$ .01) (Table 3). HCV-cured low-risk individuals developed cirrhosis at a numerically similar frequency then controls (Table 3) ($P <$ .01). Unadjusted 5-year cumulative incidence of cirrhosis was 10%, 3.6%, and 0.8% among chronic HCV, HCV cured and controls respectively (log-rank $P <$ .01). Unadjusted 5-year cumulative incidence of cirrhosis was 1.2% among HCV-cured low-risk individuals and was 0.8% among controls (Figure A) (log-rank $P <$ .01).

Decompensated Cirrhosis

Development of decompensated cirrhosis was far more common among chronic HCV individuals (n = 2285 or 11%) than among HCV-cured individuals (n = 332 or 3%) but remained more common among HCV-cured individuals than among controls (n = 913 or 1%) ($P <$ .01) (Table 3).

In models controlling for other baseline factors, risk of decompensated cirrhosis was 310% higher among chronic HCV (HR: 4.1, 95% CI: 3.6–4.7, $P <$ .01) compared to controls and was similar between HCV-cured individuals and controls (HR: 1.1, 95% CI: 0.9–1.3, $P = .26$) (Table 4).

Development of decompensated cirrhosis was far more common among HCV-cured high-risk individuals (n = 325 or 4%) than among HCV-cured low-risk individuals (n = 7 or 0.2%) ($P <$ .01) (Table 3). HCV-cured low-risk individuals developed decompensated cirrhosis at a numerically similar frequency then controls (Table 3) ($P <$ .01). Unadjusted 5-year cumulative incidence of decompensated cirrhosis was 12%, 2.6%, and 0.6% among chronic HCV, HCV-cured, and controls respectively (log-rank $P <$ .01). Unadjusted 5-year cumulative incidence of decompensated cirrhosis was 0.9% among HCV-cured low-risk individuals and was 0.6% among controls (Figure B) (log-rank $P <$ .01).

HCC

Development of HCC was far more common among chronic HCV individuals (n = 814 or 4%) than among HCV-cured individuals (n = 138 or 1%) but remained more common among HCV-cured individuals than among controls (n = 98 or 0.1%) ($P <$ .01) (Table 3).

In models controlling for other baseline factors, risk of HCC was 920% higher among chronic HCV (HR: 10.2, 95% CI: 7.5–14.0, $P <$ .01) compared to controls and remained 460% higher among HCV-cured individuals compared to controls (HR: 5.6, 95% CI: 3.9–7.9, $P <$ .01) (Table 4).

Development of HCC was far more common among HCV-cured high-risk individuals (n = 285 or 4%) than among HCV-cured low-risk individuals (n = 11 or 0.2%) ($P <$ .01) (Table 3). HCV-cured low-risk individuals developed HCC at a numerically similar frequency then controls (Table 3) ($P <$ .01). Unadjusted 5-year cumulative incidence of HCC was 3.9%, 1.6%, and 0.07% among chronic HCV, HCV-cured, and controls respectively (log-rank $P <$ .01). Unadjusted 5-year cumulative incidence of HCC was 0.5% among HCV-cured low-risk individuals and was 0.07% among controls (Figure C) (log-rank $P <$ .01).

All-Cause Mortality

All-cause mortality was far more common among chronic HCV individuals (n = 3390 or 16%) than among HCV-cured individuals (n = 468 or 4%) but was similar among HCV-cured individuals and controls (n = 3515 or 4%) (Table 3).

Table 4. Multivariate Cox Regression Models on Cirrhosis, Decompensated Cirrhosis, Hepatocellular Carcinoma, and All-Cause Mortality

Covariate[a]	Cirrhosis[b] HR (95% CI)	Decompensated cirrhosis[c] HR (95% CI)	Hepatocellular carcinoma[d] HR (95% CI)	All-cause mortality HR (95% CI)
Cohort (reference control)				
Chronic HCV	3.4 (3.0–3.9)	4.1 (3.6–4.7)	10.2 (7.5–14.0)	2.2 (2.0–2.4)
HCV Cure	1.7 (1.5–2.1)	1.1 (0.9–1.3)	5.6 (3.9–7.9)	0.6 (0.5–0.7)
BMI ≧30 kg/m^2	1.3 (1.2–1.4)	1.3 (1.2–1.4)	1.1 (0.9–1.2)	1.0 (1.0–1.1)
Alcohol disorder	1.7 (1.5–1.9)	1.4 (1.3–1.6)	1.3 (1.1–1.6)	1.3 (1.2–1.4)
Total bilirubin >1 mg/dL	2.2 (2.0–2.4)	1.9 (1.8–2.1)	1.3 (1.1–1.5)	1.3 (1.2–1.4)
Aspartate transaminase >40 U/L	2.4 (2.2–2.8)	2.4 (2.2–2.7)	2.7 (2.2–3.3)	1.5 (1.4–1.6)
Albumin <3.5 g/dL	2.7 (2.4–3.1)	2.2 (2.0–2.5)	1.8 (1.5–2.2)	2.4 (2.2–2.6)
Platelets <150 10^3/μL	4.1 (3.8–4.5)	3.8 (3.5–4.2)	3.3 (2.9–3.9)	1.6 (1.5–1.7)
Diabetes	1.3 (1.2–1.4)	1.3 (1.2–1.4)	1.2 (1.1–1.5)	1.6 (1.5–1.7)
Chronic hepatitis B	4.2 (3.2–5.5)	1.3 (0.9–1.8)	3.3 (2.1–5.4)	1.2 (0.9–1.6)

BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio.
[a]Controls for age, sex, race/ethnicity, drug disorder, tobacco status, HIV, hepatitis B status, alanine transaminase, statin, aspirin, clopidogrel, ACE-inhibitor.
[b]Excludes baseline cirrhosis.
[c]Excludes baseline decompensated cirrhosis.
[d]Excludes baseline hepatocellular carcinoma.

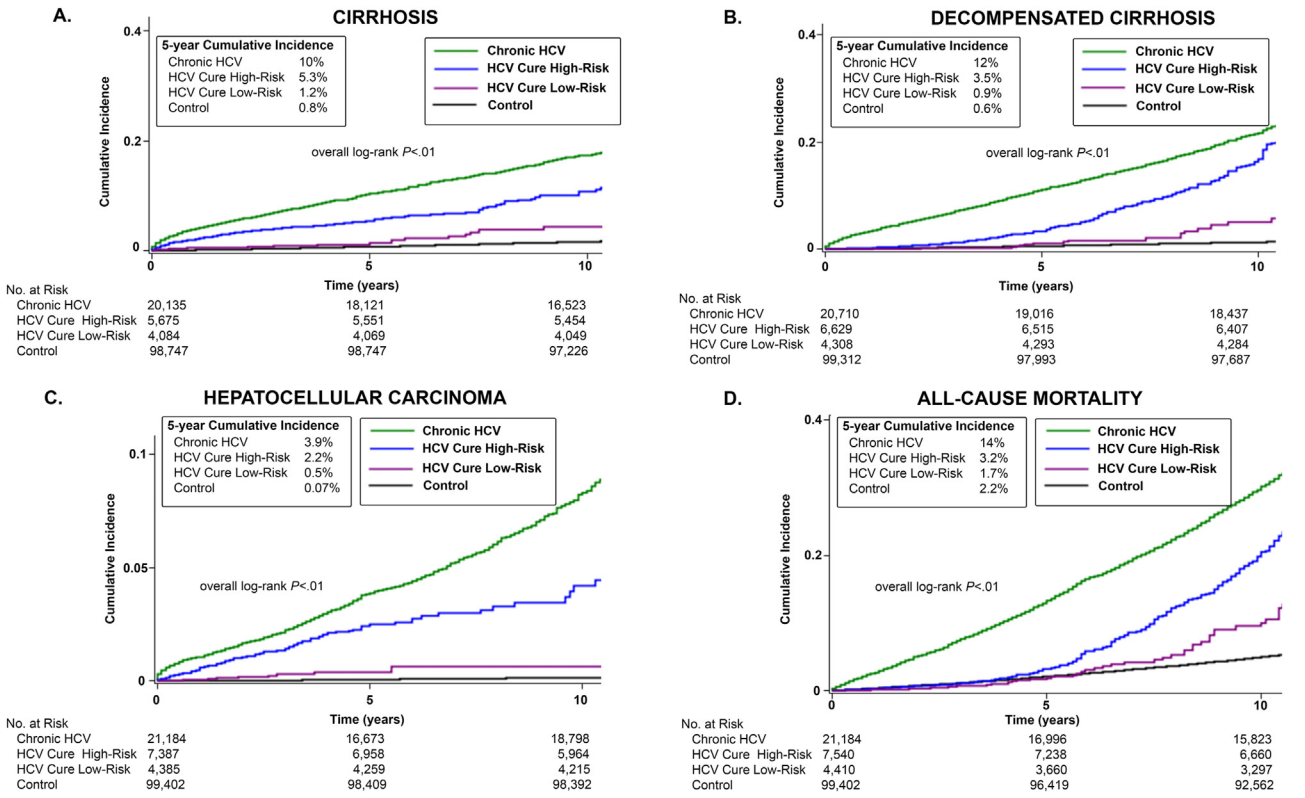

Figure. Cumulative incidence of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and all-cause mortality by cohort. Figures A, B, C, and D display cumulative incidence of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and all-cause mortality respectively among chronic HCV, HCV-cured high-risk, HCV-cured low-risk, and controls. Log-rank *P* values displayed are for comparisons of all cohorts. HCV, hepatitis C virus.

In models controlling for other baseline factors, risk of all-cause mortality was 120% higher among chronic HCV (HR: 2.2, 95% CI: 2.0–2.4, $P < .01$) compared to controls and was 40% *lower* among HCV-cured individuals compared to controls (HR: 0.6, 95% CI: 0.5–0.7, $P < .01$) (Table 4).

All-cause mortality was far more common among HCV-cured high-risk individuals (n = 437 or 6%) than among HCV-cured low-risk individuals (n = 31 or 0.7%) ($P < .01$) (Table 3). All-cause mortality was lower among HCV-cured low-risk individuals (n = 31 or 0.7%) than that of controls (n = 3515 or 4%) ($P < .01$). Unadjusted 5-year cumulative incidence of all-cause mortality was 1.7% among HCV-cured low-risk individuals and was 2.2% among controls (Figure D) (log-rank $P < .01$).

Discussion

In our large representative cohort study, where for the first time the benefits of HCV cure were compared not only to lack of cure but also to matched HCV never-infected controls, HCV cure resulted in a reduced risk of incident cirrhosis, decompensated cirrhosis, HCC and all-cause mortality compared to no cure, but did not result in risk-reduction down to controls. Our models show that HCV cure reduced risk of poor liver outcomes but that HCV cured individuals still had a 70% higher risk of cirrhosis, 10% higher risk of decompensated cirrhosis and a 460% higher risk of HCC compared to controls. In addition, we found that variables at the time of HCV cure for significant liver disease and/or liver disease cofactors of NAFLD, alcohol-associated liver disease and/or chronic HBV could stratify around 37% of cured individuals into a low-risk group whose risk of poor outcomes are numerically similar to or even lower than controls and therefore may potentially be discharged from specialty clinics and HCC surveillance.

The cumulative incidence of all-cause mortality was numerically similar between HCV cure and control individuals, was lower among HCV-cured low-risk individuals compared to controls and in multivariate Cox proportional hazard models, was also lower among HCV-cured individuals compared to controls. We speculate that this is because of the engagement in care from individuals who achieve HCV cure. Some of the HCV treatment regimens utilized to achieve cure included use of pegylated interferon and/or ribavirin, both of which can result in cardiac dysfunction.[25,26] Therefore, HCV treating providers routinely perform cardiac testing before initiation of HCV treatment with these medications and potentially identified and intervened on asymptomatic coronary artery disease. Further, in KPNC most HCV treatment is provided by gastroenterologists and therefore there may have been more concomitant colorectal cancer screening among individuals in the HCV-cured cohort.

The French Hepather cohort, Carrat et al[27] failed to demonstrate lower rate of decompensated cirrhosis with HCV cure. However, a South American study found that HCV cure was significantly associated with a lower incidence of decompensation (HR: 0.3, 95% CI: 0.1–0.8; $P = .02$) in a cohort of 1760 individuals followed for a median of 26 months.[28] The later study results are similar to ours where we noted a 300% reduction in development of decompensated cirrhosis from HCV cure compared to no cure in multivariate analyses. In a large observational cohort analysis from the Veterans Affairs Hepatitis C Clinical Case Registry restricted to HCV individuals without cirrhosis, they observed between a 66% and 71% risk-reduction in all-cause mortality depending on baseline FIB-4 score from HCV cure compared to no cure.[29] In our study that included individuals with baseline cirrhosis and decompensated cirrhosis, we found a similar relative risk reduction from HCV cure of 75% at 5 years. While these studies with similar results reinforce our results, no study before this one has provided the quantification of these benefits of HCV cure compared to an HCV never-infected control population.

Using Veterans Affairs Hepatitis C Clinical Case Registry data, Kanwal et al[12] found that compared to chronic HCV patients, HCV cure resulted in a significant HCC risk reduction with adjusted HR 0.28 (95% CI: 0.22–0.36). The authors further noted that among HCV cure patients, the annual incidence of HCC was higher among patients with cirrhosis (defined using International Classification of Disease-9 or 10 codes) compared to those without at time of treatment (1.82 vs 0.34/100 person-years).[12] These data are largely the basis for the American Association for the Study of Liver Diseases recommendation that all HCV-cured patients with cirrhosis before treatment should continue HCC surveillance.[17] Our results are concordant with this work but suggest that presence or absence of cirrhosis alone at the time of HCV treatment may not be the only approach to predicting post-HCV cure HCC development. In a cost-effectiveness analysis, Lin et al[30] determined that in patients with cirrhosis, HCC surveillance was justified if the HCC risk was greater than 1.5%/year and among individuals without cirrhosis, a separate cost-effectiveness analysis suggested that threshold should be 0.2%/year.[31] Our identified HCV-cured low-risk group had an estimated annual incidence of 0.1%/year of HCC, justifying removal of HCC surveillance from this group.

There are several limitations with our study. Due to improvements of HCV antiviral treatment over the study period, it was inevitable that follow-up duration was shorter in individuals with HCV cure than in chronic HCV and controls. It is unlikely, however, that this follow-up difference had a substantial effect on our results because the clinical events followed linear patterns over time and controls were captured 3:1 at both the time of entry into chronic HCV and HCV-cured cohorts. Furthermore, the outcome of cirrhosis was likely more robustly evaluated later during the study period as the availability of direct-acting antivirals against HCV led to a KPNC-wide outreach to evaluate and stage fibrosis among chronic HCV individuals as did the widespread availability of transient elastography. Likely, this results in an underdiagnosis of cirrhosis, particularly among chronic HCV and their control individuals; therefore, it suggests that the reported benefits of HCV cure are underestimated in this study. There is a selection bias in the chronic HCV cohort as not all KPNC adult members underwent HCV testing, particularly as the United States Preventive Services Taskforce

recommendation to expand HCV screening to all adults 18–79 years old occurred only in March of 2020. While this may also lead to a concern that the HCV never infected control cohort may contain chronic HCV individuals, we are reassured that by June 1, 2019 (study enrollment end), KPNC had achieved > 90% HCV screening among those born between 1945 and 1965 (ie, "baby-boomers"), and internal data show that 31% of women and 23% of men not in the "baby-boomer" cohort had already been tested for HCV and the chronic infection rate is extremely low at 0.06% and 0.14% respectively. In addition, since the HCV never-infected control cohort was matched by age, the vast majority were born between 1945 and 1965 (median age of the control group was 54 years with an interquartile range of 45–62 years). Therefore, we believe the possibility of inadvertently having HCV-positive patients in the HCV never-infected control group is very low. Finally, the approach of defining NAFLD cofactor at the time of HCV cure was purposefully chosen to be simplistic and easily applied instead of application of more involved scores like the Hepatic Steatosis Index or the DSI. This likely led to an overly cautious definition of the low-risk stratification of the HCV cured cohort and future studies can consider different definitions.

Conclusion

In conclusion, our study indicates that HCV cure provides significant health benefits but does not universally return risk of poor outcomes to that of the general population. An assessment at the time of HCV cure for significant liver disease and/or liver disease cofactors of NAFLD, alcohol-associated liver disease and/or chronic HBV can identify low-risk individuals whose risk of poor outcomes are similar to HCV-never infected individuals and who therefore may potentially be discharged from specialty clinics and HCC surveillance.

References

1. Rosenberg ES, Rosenthal EM, Hall EW, et al. Prevalence of hepatitis C virus infection in US states and the District of Columbia, 2013 to 2016. JAMA Netw Open 2018;1:e186371.
2. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463–472.
3. Singal AG, Volk ML, Jensen D, et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280–288, 288.e1.
4. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138:513–521, 521.e1-6.
5. Razavi H, Waked I, Sarrazin C, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat 2014;21 Suppl 1:34–59.
6. Vezali E, Aghemo A, Colombo M. A review of the treatment of chronic hepatitis C virus infection in cirrhosis. Clin Ther 2010;32:2117–2138.
7. Pecoraro V, Banzi R, Cariani E, et al. New direct-acting antivirals for the treatment of patients with hepatitis C virus infection: a systematic review of randomized controlled trials. J Clin Exp Hepatol 2019;9:522–538.
8. Aleman S, Rahbin N, Weiland O, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infect Dis 2013;57:230–236.
9. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology 2007;45:579–587.
10. Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol 2010;52:652–657.
11. Fernández-Rodríguez CM, Alonso S, Martinez SM, et al. Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: outcomes and factors predicting response. Am J Gastroenterol 2010;105:2164–2172; quiz 2173.
12. Kanwal F, Kramer J, Asch SM, et al. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 2017;153:996–1005.e1.
13. Nahon P, Bourcier V, Layese R, et al. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. Gastroenterology 2017;152:142–156.e2.
14. Simmons B, Saleem J, Heath K, et al. Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. Clin Infect Dis 2015;61:730–740.
15. van der Meer AJ, Feld JJ, Hofer H, et al. Risk of cirrhosis-related complications in patients with advanced fibrosis following hepatitis C virus eradication. J Hepatol 2017;66:485–493.
16. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584–2593.
17. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723–750.
18. Hedderson MM, Ferrara A, Avalos LA, et al. The Kaiser Permanente Northern California research program on genes, environment, and health (RPGEH) pregnancy cohort: study design, methodology and baseline characteristics. BMC Pregnancy Childbirth 2016;16:381.
19. Philip G, Djerboua M, Carlone D, et al. Validation of a hierarchical algorithm to define chronic liver disease and cirrhosis etiology in administrative healthcare data. PLoS One 2020;15:e0229218.

20. Ajmera V, Cepin S, Tesfai K, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. J Hepatol 2023;78:471–478.
21. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. Lancet Diabetes Endocrinol 2022;10:284–296.
22. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol 2019;71:793–801.
23. Lee YH, Cho Y, Lee BW, et al. Corrigenda: table correction. Nonalcoholic fatty liver disease in diabetes. Part I: epidemiology and diagnosis. Diabetes Metab J 2019;43:731.
24. McHenry S, Park Y, Browning JD, et al. Dallas steatosis index identifies patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2020;18:2073–2080.e7.
25. Choy-Shan A, Berezovskaya S, Zinn A, et al. Nonischemic cardiomyopathy related to pegylated interferon and ribavirin. Eur J Gastroenterol Hepatol 2009;21:1438–1440.
26. Condat B, Asselah T, Zanditenas D, et al. Fatal cardiomyopathy associated with pegylated interferon/ribavirin in a patient with chronic hepatitis C. Eur J Gastroenterol Hepatol 2006;18:287–289.
27. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet 2019;393:1453–1464.
28. Mendizabal M, Piñero F, Ridruejo E, et al. Disease progression in patients with hepatitis C virus infection treated with direct-acting antiviral agents. Clin Gastroenterol Hepatol 2020;18:2554–2563.e3.
29. Backus LI, Belperio PS, Shahoumian TA, et al. Direct-acting antiviral sustained virologic response: impact on mortality in patients without advanced liver disease. Hepatology 2018;68:827–838.
30. Lin OS, Keeffe EB, Sanders GD, et al. Cost-effectiveness of screening for hepatocellular carcinoma in patients with cirrhosis due to chronic hepatitis C. Aliment Pharmacol Ther 2004;19:1159–1172.
31. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–1022.

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Ethical Statement:
This study was approved by the Kaiser Permanente Northern California Institutional Review Board.

Data Transparency Statement:
Raw data collected in this study will not be made available to any researcher for purposes of reproducing the results per Kaiser Permanente Division of Research Policy. Methods used in the analysis used to conduct the research will be made available to any researcher for purposes of reproducing the analysis on their own data. Please contact corresponding author.

Reporting Guidelines:
None.