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Infection With Hepatitis C Virus Genotype 3 is an Independent Risk Factor for End-stage Liver Disease, Hepatocellular Carcinoma, and Liver-related Death

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Abstract

Background & Aims—Few studies have examined factors associated with disease progression in hepatitis C virus (HCV) infection. We examined the association of 11 risk factors with adverse outcomes in a population-based prospective cohort observational study of Alaska Native/American Indian persons with chronic HCV infection.

Methods—We collected data from a population-based cohort study of liver-related adverse outcomes of infection in American Indian/Alaska Native persons with chronic HCV living in Alaska, recruited from 1995 through 2012. We calculated adjusted hazard ratios (aHR) and 95% CIs for end-stage liver disease (ESLD; presence of ascites, esophageal varices, hepatic encephalopathy, or coagulopathy), hepatocellular carcinoma (HCC), and liver-related death using a Cox proportional hazards model.

Results—We enrolled 1080 participants followed for 11,171 person-years (mean, 10.3 years); 66%, 19%, and 14% were infected with HCV genotypes 1, 2, and 3, respectively. On multivariate analysis, persons infected with HCV genotype 3 had a significantly increased risk of developing

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all 3 adverse outcomes. Their aHR for ESLD was 2.1 (95% CI, 1.5–3.0), aHR for HCC was 3.1 (95% CI, 1.4–6.6), and aHR for liver-related death was 2.4 (95% CI, 1.5–4.0) compared to genotype 1. Heavy alcohol use was an age-adjusted risk factor for ESLD (aHR, 2.2; 95% CI, 1.6–3.2), and liver-related death (aHR: 2.9; 95% CI, 1.8–4.6). Obesity was a risk factor for ESLD (aHR, 1.4; 95% CI, 1.0–1.9, and diabetes was a risk factor for ESLD (aHR, 1.5; 95% CI, 1.1–2.2). Male sex was a risk factor for HCC (aHR, 3.6; 95% CI, 1.6–8.2).

Conclusions—In a population-based cohort study of American Indian/Alaska Native persons with chronic HCV infection, we found those infected with HCV genotype 3 to be at high risk for ESLD, HCC, and liver-related death.

Keywords

Hepatitis C Outcome; AK-HEPC; liver cancer risk; American Indian/ Alaska Native

Introduction

Infection from Chronic hepatitis C virus (HCV) is a significant cause of cirrhosis, hepatocellular carcinoma and liver related death worldwide, with an estimated 140 to 170 million persons infected. (1) In the United States (US), an estimated 2% to 3% of persons born between 1945 and 1965 have chronic hepatitis C with 2 to 3 million persons infected. (2) Due to the paucity of large population-based prospective cohort studies of persons with chronic hepatitis C, the factors associated with progression of disease such as viral genotype, viral load, mode of acquisition of infection and previous exposure to hepatitis B virus to mention a few, are not well elucidated. Since 1995, the Alaska Native Tribal Health Consortium (ANTHC), Liver Disease and Hepatitis Program (LDHP) in collaboration with the Arctic Investigations Program and the Division of Viral Hepatitis of the Centers for Disease Control and Prevention (CDC) have been conducting a population-based cohort study (AKHEPC) of liver related adverse outcomes of chronic HCV infection in American Indian/Alaska Native (AI/AN) persons residing in Alaska. We previously determined that the AK-HepC cohort had similar risk factors for acquisition and HCV genotype distribution when compared to the National Health and Nutritional Examination Survey (NHANES) conducted in 1994 of infected persons from the general US population.(3, 4) Previously we analyzed outcome both prospectively and retrospectively through 2006 in this cohort and compared them to persons who recovered from HCV who were recruited at the same time. We found that end stage liver disease (ESLD) was associated with older age and alcohol usage. We also found that compared with HCV genotype 2, genotype 3 infection was associated with a higher risk of ESLD on multivariate analysis, but not compared with genotype 1.(5) For this analysis, we included all persons recruited from 1995–2012 and only included data obtained prospectively starting from the time of consent. We examined 11 risk factors for any association with ESLD, HCC and liver related death. Herein, we present the results of this study.

Methods

ANTHC coordinates ATHS healthcare throughout the state of Alaska. Further details of the population and health care delivery system have been described previously and in the

supplemental Text.(4) Electronic Health (EHR) records are used in these statewide Tribal facilities. Testing for anti-HCV was conducted at the laboratory at the Alaska Native Medical Center (ANMC); all positive results were automatically reflexed for HCV RNA testing then downloaded into our HCV computerized Registry. All patients in the HCV registry, whether they are participants in the study or not, are mailed a letter every six months reminding them to go to their local clinic to get tested for liver function tests. A list of patients in their area with chronic HCV are sent to each regional facility and updated twice yearly. Testing for anti-HCV is conducted at the laboratory at ANMC and all positive results are automatically reflexed for HCV RNA testing then downloaded into the HCV Registry. The HCV registry includes extensive laboratory data, clinical data and demographic data and is used primarily for management of infected persons. All pertinent laboratory tests performed at ANMC on patients in the HCV registry are automatically downloaded into the AK-HepC database twice weekly. Laboratory data performed at the regional hospitals and clinics are added into the data base at the time of field clinic visits and by access given to our program to these facilities Electronic Health Records systems. The LDHP works with Tribal providers throughout Alaska and conducts field hepatology clinics at all regional hospitals once or twice a year. We use telemedicine, Vidyo® clinics, tele-radiography and other means to care for HCV-infected patients. Since the beginning of this study, all patients who are eligible have been offered FDA-approved drugs for treatment at the time based on guidelines from the American Association for the Study of Liver Diseases/ Infectious Disease Society of America (AASLD/IDSA).(6) During the period when interferon-based therapies were the only licensed regimens available, over 50% of patients were deemed eligible candidates for treatment, but most refused.(7) However, in the era of direct acting antiviral agents (DAA) licensed in the US since the fall of 2014, almost all eligible patients now agree to therapy and are currently offered DAA regardless of stage of liver fibrosis. All patients in the registry who were both anti-HCV positive and HCV RNA positive for at least one year have been invited to join the AK-HepC study. The study was approved by the Alaska Area and CDC Investigational Review Boards. The study was also approved by all regional tribal health organization boards in Alaska. All participants provided written informed consent.

At the time of AK-HepC study enrollment, study nurses conducted an extensive interview of each participant to obtain information on risk factors and demographic data that are reviewed in our previous publication.(5) Information was obtained directly from the HCV registry, by chart review including ICD9 liver related diagnosis and review of the State of Alaska Death Tapes from 1995 through 2012. In addition, an extensive chart review was performed on each participant at the end of the study period to examine for clinical evidence of liver disease that occurred during the study period. We defined advanced fibrosis as either a Knodell fibrosis score ≥3, equivalent to Metavir fibrosis of F3/F4, on liver biopsy or APRI ≥1.5 which has a specificity of approximately 90%.(8) ESLD was defined by the presence of one or more of the following: ascites, esophageal varices, hepatic encephalopathy, or coagulopathy (INR ≥1.2 or platelet count <130,000 on at least two occasions more than 2 months apart). The diagnosis of HCC was made by pathological confirmation or on radiographic imaging exam (CT, US or MRI) consistent with a mass lesion with typical features for HCC including enhancing during the arterial phase. Liver related death was

defined as death with immediate cause from a complication of liver disease or death with liver disease listed as a contributing cause in medical chart review and death certificate and also included persons who underwent liver transplant. We evaluated the cohort for eleven different potential contributing factors that might be associated with each of the four adverse outcomes. These included age at start of enrollment, gender, residence (urban or rural), risk factor for acquisition of HCV (blood transfusion prior to 1992, injecting drug use or other), HCV genotypes 1, 2 and 3, presence of hepatitis B core antibody (anti-HBc) in the absence of hepatitis B surface antigen (HBsAg), heavy alcohol consumption (defined as > 50 grams average/day at enrollment), tobacco smoker, obesity as defined by a BMI > 30, Type II diabetes, and HCV RNA level. HCV RNA level was divided into five categories: < 50,000, 50,000 to <200,000, 200,000 to <1 million, 1 million to < 5 million, and > 5 million IU/ml. Due to the few persons in the AK-HepC cohort with active hepatitis B or HIV infection, persons with these co-infections were excluded from analysis.

Laboratory Testing

Detection of anti-HCV antibodies (EIA2.0 [Abbott Laboratories]), and HCV RNA (COBAS®Taqman®HCV Test, v2.0 [Roche Molecular Diagnostics]), were performed at the Alaska Native Medical Center laboratory (Anchorage, Alaska). HCV viral genotype was determined by real-time polymerase chain reaction by Quest Diagnostics (Hepatitis C Genotype, LIPA®).

Statistical Analysis

The starting point for all survival analyses was the date of the confirmatory HCV testing. Age was calculated at the start of clinical follow-up and divided into quartiles (< 30 years, 30–39, 40–49, and ≥ 50 years). For risk factors we divided the cohort into persons with a pre-1993 blood transfusion (BT), persons with a history of intravenous drug use (IVDU) and all others. Persons living in Anchorage, Juneau, Fairbanks and surrounding areas were considered urban residents with all others classified as rural. For persons treated for HCV, the end of follow-up was defined as the treatment start date. The end of follow-up among those with an outcome was the date of detection of ESLD, HCC, liver related death (primary outcomes) or advanced fibrosis (secondary outcome). Among those without an outcome, the date of their last clinical follow-up or their date of death was used. For ESLD, the date of their first ESLD objective finding was used. We used the Cox-Proportional hazards model to report uni-variable and multi-variable p-values. We used a purposeful forward selection method to build a final multi-variable model. Factors with a uni-variable p-value < 0.25 were considered in the building of the multi-variable models. Variables were considered confounders and remained in the model if their exclusion changed the value of the coefficients of interest by more than 15%. All reported p-values are two-sided, were not adjusted for multiple testing, and a value < 0.05 was considered statistically significant. Kaplan-Meier survival estimates were used to report the probabilities of the outcome after 15 years of follow-up.

Results

Among 1,132 persons found to have chronic HCV through 2012, 1080 (95.4%) were enrolled. Table 1 gives the demographic, risk factors, clinical, social and laboratory characteristics of this cohort. Two thirds of participants (66%) were infected with HCV genotype 1, 90% with 1a, while 19% and 14% were infected with HCV genotype 2, and 3, respectively. At study entry, 22% of genotype 3 patients had an elevated APRI score (≥ 1.5) which did not differ from 21% and 23% in genotype 1 and 2 patients, respectively. The 1080 persons were followed prospectively for 11,171 person years (mean of 10.3 years). The median age at the time of enrollment was 41 years and 51% of participants were female. HIV co-infection was found in 29 and HBsAg in 10; as mentioned in the Methods, these patients are not included in the outcome analysis. A total of 157 patients received interferon-based antiviral treatment, of which 76 achieved SVR and were censored from further analysis after that time. Over half of the patients were tobacco smokers and 10% had diabetes. Daily heavy alcohol intake was reported by 14% of participants. Over half of the patients lived in cities with a population above 10,000 (urban).

During the study period, 341 persons developed advanced fibrosis, 210 ESLD, 40 HCC and 96 liver related death, with some patients developing more than one of these adverse outcomes. Of the 341 patients with advanced fibrosis, 190 (56%) were identified by liver biopsy, and 151 (44%) were identified by their APRI scores. Of the 40 patients with HCC, 39 met the definition of HCC we used in the methods. One patient with 4 cm lesion of the liver on US, liver failure, history of stroke and multiple contractures could not fit comfortably into the CT or MRI scanners. He developed a second lesion several months later and died of liver failure. We included him as a probable case of HCC.

Table 2 shows the results of Hazard Ratios (HRs) in univariate analysis for the 11 risk factors for all three primary outcomes. Using HCV genotype 1 as the referent, persons infected with genotype 3 were significantly more likely to develop ESLD and liver related death and those with genotype 2 were less likely to develop ESLD. Developing ESLD was significantly associated with age at start of follow-up, HCV genotype 3, heavy alcohol usage, and type II diabetes. HCC was associated with male sex and age at start of follow-up. Liver related death was associated with age, genotype 3, presence of Hep B Core antibody, DM2 and heavy alcohol usage. Results for the secondary outcome of advanced fibrosis were very similar to the results for ESLD and are included in supplemental Tables 1 and 2.

The multi-variable model for ESLD identified for HCV genotype (1, 2, and 3), age at cohort entry, heavy alcohol use (average >50 grams/day), obesity (body mass index [BMI] ≥30), and type II diabetes (DM2) (Table 3) as factors significantly associated with risk of ESLD. The model for HCC identified HCV genotype, age at cohort entry, and sex as risk factors. HCV genotype, age at cohort entry, and heavy alcohol use were significant factors associated with liver related death. Persons infected with HCV genotype 3 were significantly more likely to develop all three adverse outcomes, ESLD, HCC and liver related death than those infected with HCV genotype 1. After 15 years of clinical follow-up, the probability of developing ESLD for those infected with HCV genotype 3 was 48% and for liver related death was 24%. Older age at enrollment was also associated with all three adverse outcomes.

The increases in risk for developing ESLD were heavy alcohol use (aHR: 2.2; CI: 1.6–3.2), obesity (aHR: 1.4; CI: 1.0–1.9; p = 0.03), and DM2 (aHR: 1.5; CI: 1.0–2.3; p = 0.03). The risk for developing HCC was higher for males than females (aHR: 3.6; CI: 1.6–8.2). Persons with heavy alcohol use were at increased risk for liver related death (aHR: 2.9; CI: 1.8–4.6) (Table 3). Several important risk factors were not associated with any of the adverse outcomes on multi-variable analysis. Surprisingly, HCV RNA level had no effect on any of the outcomes. The risk factor for acquisition also did not have any effect, nor did the presence of anti-HBc in the absence of HBsAg, which could indicate occult HBV.

Discussion

To our knowledge, the AK-HEPC study is the largest and longest population-based cohort study to examine the long-term outcome of chronic HCV infection. This population-based study of over 1,000 participants (94% of the known Alaska Native Persons with chronic HCV infection in the state), followed for 11,171 person years, a mean of over 10 years, was designed to prospectively examine adverse events due to HCV infection. The study encompasses a large amount of clinical and laboratory data coupled with baseline risk factor, electronic medical records, State of Alaska death records and other data collected at entry plus personal clinical statewide follow-up by the providers and nurses on our LDHP team. We found an important association with the adverse outcomes of ESLD, HCC and liver related death in those infected with HCV genotype 3 compared to genotype 1. In the AK-HEPC cohort 14% have genotype 3. In this cohort, within 15 years of diagnosis, two-thirds of those with genotype 3 had progressed to advanced fibrosis, half to ESLD, one quarter had died or had received a liver transplant and almost 1 in 10 developed HCC.

Recently, a retrospective study in the VA using a search of their HCV Clinical Registry and ICD9 codes, found that HCV genotype 3 was associated with a 31% higher risk of developing cirrhosis and 80% higher risk of developing HCC compared with genotype 1 patients.(9) to the authors and our knowledge, the VA study was the first to show that HCV genotype 3 had a higher risk of cirrhosis and HCC than genotype 1. We confirm their findings of an increased risk of HCC and ESLD and extend this significant risk to include advanced fibrosis and liver related death. In their discussion, the authors commented on the limitation of their study as it was retrospective in nature and that a large prospective cohort study with sufficient follow-up was unlikely to be conducted due to cost and feasibility. However, we actually have conducted such a study as reported herein. The VA study relied on ICD9 codes whereas we actively followed participants prospectively. One third of the patients in the VA Clinical Registry did not have HCV genotype testing done, as opposed to only 4 of 1,080 persons in our study, and the VA study did not eliminate persons with HIV or HBV co-infection, plus included patients who were previously treated for HCV. Genotype 3 may excerpt some of its adverse effects by increasing liver steatosis independent of diabetes or obesity resulting in more rapid liver fibrosis which then leads to higher rates of cirrhosis and HCC.(10) In a previous study looking at factors associated with the amount of fibrosis on liver biopsy, we found that steatosis was prominent in those with genotype 3 and an independent risk factor. Fibrosis and steatosis were more advanced in genotype 3 patients compared to genotypes 1 and 2 when adjustment for BMI and diabetes was performed.(11) As seen in Table 2, there were no differences in adverse outcomes between urban and rural

areas or differences in the distribution of the important risk factors of HCV genotype, obesity, risk exposure, or alcohol use.

Surprisingly, we found that HCV RNA level was not associated with any of the outcomes in multi-variable analysis. In performing this analyses, we divided participants into five groups based on their initial HCV RNA level, ranging from <50,000 to > 5 million IU/ml, with well over 100 participants in each group. This was in contrast to what has been found in studies of chronic hepatitis B virus (HBV) infection, our long-term prospective chronic hepatitis B outcome study in AN/AI persons, where higher levels of HBV DNA, especially above 20,000 IU/ml, are a significant risk factor in developing HCC and cirrhosis.(12–14). It is not clear why viral level in HCV was not found to be associated with outcome. It is possible that the vigorous immune response evoked by the presence of HCV, regardless of viral level, is the critical factor in promoting progression, rather than the activity of the virus itself. We also found that HCV infected persons with occult HBV infection, those negative for HBsAg but positive for anti-HBc, had no greater risk of developing any of the adverse outcomes.

There are a few limitations to our study. First of all, all participants are AI/AN persons, but, since the characteristics in the AK-HepC cohort did not differ from those found in the NHANES study of the general US population with regards to prevalence, distribution of risk factors and prevalence of HCV genotypes,(4) it is less likely that significant differences in risk factors for disease outcome are present. In addition, response to interferon-based therapy are similar to previous US studies and registration trials.(15)

In conclusion, our study has yielded some important findings regarding the risk factors for progression of HCV to adverse life threatening outcomes. The most striking finding was that HCV genotype 3 has significant risk for the development of all adverse outcomes studied, suggesting that persons with genotype 3 HCV infection should be prioritized for treatment. However, currently genotype 3 is the most difficult HCV genotype to treat, especially for patients with cirrhosis or who were previously treated and failed to achieve SVR. Fortunately, new pan-genotype oral antivirals are on the horizon and could be available soon, offering the opportunity to better target patients with HCV genotype 3.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of persons chronically infected with the hepatitis C virus amongst American Indian/Alaska Native (AI/AN) persons (AK-Hep C cohort, Alaska, 1995–2012).

Characteristic	Level	N (%) or Median (IQR) PCR Positive (n = 1081)
Age at Start of Clinical Follow-up		41 (34, 47)
Sex	Female	549 (51%)
	Male	532 (49%)
Death	Yes	262 (24%)
	No	819 (76%)
Recovered from HCV	Yes	
	No	
HCV Genotype [a]	1	713 (66%)
	1a	551 (51%)
	1b	143 (13%)
	1a/1b or 1	19 (2%)
	2	199 (19%)
	1/2	3 (0.3%)
	3	156 (14%)
	4	6 (1%)
HCV RNA level at Start of Clinical Follow-up [b] (IU/ml)	<50,000	177 (17%)
	50,000 – <200,000	202 (19%)
	≥200,000 – < 1 Mil	276 (26%)
	≥1 Mil – < 5 Mil	286 (27%)
	≥5 Mil	127 (12%)
Known HIV Coinfection		29 (3%)
Hepatitis B core antibody		227 (21%)
Liver Biopsy Done	Yes	456 (42%)
	No	625 (58%)
Residence	Urban	631 (58%)
	Rural	450 (42%)
Risk Exposure	Intravenous Drug Use	614 (57%)
	Pre-1992 Blood Transfusion	122 (11%)
	Other	345 (32%)
Treated for HCV Infection	Yes	157 (15%)
	No	923 (85%)

Characteristic	Level	N (%) or Median (IQR) PCR Positive (n = 1081)
Daily ETOH [c]	Heavy (> 50 gm/day)	147 (14%)
	Moderate (30–50 gm/day)	164 (15%)
	Light (10–20 gm/day)	270 (25%)
	None	490 (46%)
Known Smoker	Yes	547 (51%)
	No	534 (49%)534 (49%)
Known Type II Diabetes	Yes	109 (10%)
	No	972 (90%)
Advanced Fibrosis		341 (32%)
HCC		40 (4%)
ESLD		210 (19%)

[a] 4 persons positive for HCV RNA are missing an HCV genotype.

[b] 13 people positive for HCV RNA were missing an RNA level, positive result only reported.

[c] 10 persons are missing alcohol use.

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Table 2

Univariate risk factors for end stage liver disease (ESLD), hepatocellular carcinoma (HCC) and liver-related death among HCV infected American Indian/Alaska Native (AI/AN) persons (AK-Hep C cohort, 1995–2012). Persons successfully treated were censored at the time of treatment.

Risk Factor	Level	ESLD		HCC		Liver Related Death and Transplant	
		Hazard Ratio	P-value	Hazard Ratio	P-value	Hazard Ratio	P-value
Gender	M	1.31 (1.0, 1.7)	0.06	4.17 (2.0, 8.8)	.0002	1.44 (1.0, 2.2)	0.08
	F	ref		ref		ref	
Age at Start of Clinical Follow-up	<30	0.17 (0.1, 0.3)	<.0001	0.0	<.0001	0.04 (0.01, 0.2)	<.0001
	30–39	0.37 (0.2, 0.6)		0.04 (0.0, 0.1)		0.21 (0.1, 0.4)	
	40–49	0.59 (0.4, 0.9)		0.28 (0.1, 0.6)		0.35 (0.2, 0.6)	
	50+	ref		ref		ref	
Residence	Rural	0.97 (0.7, 1.3)	0.83	1.19 (0.6, 2.3)	0.58	1.04 (0.7, 1.6)	0.87
	Urban	ref		ref		ref	
Risk Factor	BT	0.98 (0.6, 1.6)	0.76	2.60 (1.0, 6.8)	0.12	1.28 (0.7, 2.4)	0.56
	IVDU	0.9 (0.7, 1.2)		1.33 (0.6, 3.0)		0.94 (0.6, 1.5)	
	Other	ref		ref		ref	
Genotype	1	ref	.0004	ref	0.09	ref	0.01
	2	0.65 (0.4, 1.0)		0.84 (0.3, 2.2)		1.18 (0.7, 2.0)	
	3	1.61 (1.2, 2.3)		2.15 (1.0, 4.5)		2.07 (1.3, 3.4)	
Hep B Core Positive	Yes	0.97 (0.7, 1.3)	0.86	1.49 (0.8, 3.0)	0.25	1.57(1.0, 2.4)	0.04
	No	ref		ref		ref	
Heavy ETOH	Yes	2.04 (1.5, 2.8)	<0.0001	0.66 (0.2, 1.8)	0.42	2.26 (1.5, 3.5)	0.0002
	No	ref		ref		ref	
Tobacco Smoking Status	Current	0.79 (0.6, 1.5)	.40	0.71 (0.3, 1.8)	.34	0.76 (0.4, 1.4)	0.58
	Previous	0.91 (0.6, 1.5)		1.48 (0.5, 4.3)		1.01 (0.5, 2.3)	
	No	ref		ref		ref	
Obesity (BMI ≥ 30)	Yes	1.22 (0.9, 1.6)	0.18	1.06 (0.5, 2.1)	0.87	0.79 (0.5, 1.2)	0.30

Risk Factor	Level	ESLD		HCC		Liver Related Death and Transplant	
		Hazard Ratio	P-value	Hazard Ratio	P-value	Hazard Ratio	P-value
Type II Diabetes	No	ref	0.03	ref	0.43	ref	0.04
	Yes	1.53 (1.1, 2.2)		1.43 (0.6, 3.4)		1.69 (1.0, 2.8)	
	No	ref		ref		ref	
RNA Level	<50,000	0.76 (0.4, 1.3)	0.62	0.65 (0.1, 3.2)	0.71	0.90 (0.4, 2.3)	0.38
	50,000 – <200,000	.81 (0.5, 1.4)		1.55 (0.4, 5.7)		1.31 (0.6, 3.0)	
	≥200,000 – < 1 Mil	0.94 (0.6, 1.5)		1.44 (0.4, 5.1)		1.17 (0.5, 2.6)	
	≥1 Mil – < 5 Mil	1.04 (0.6, 1.7)		1.41 (0.4, 5.1)		1.68 (0.8, 3.7)	
	≥5 Mil	ref		ref		ref	

Table 3

Multi-variable risk factor results for the development of end stage liver disease (ESLD), hepatocellular carcinoma (HCC) and liver-related death. Only statistically significant risk factors remained in the multi-variable models.

Outcome	Risk Factor	Level	Hazard Ratio	P-value	Proportion who have had Outcome at 15 Years of Clinical Follow-up
ESLD	Age at Start of Clinical Follow-up	<30	0.13 (0.07, 0.27)	<0.0001	18.2%
		30–39	0.27 (0.18, 0.42)		25.4%
		40–49	0.52 (0.35, 0.78)		33.2%
		50+	ref		40.2%
	Heavy ETOH	Yes	2.24 (1.59, 3.16)	<0.0001	43.5%
		No	ref		27.4%
	HCV Genotype	1	ref	<0.0001	28.2%
		2	0.61 (0.38, 0.98)		21.8%
		3	2.11 (1.48, 3.00)		47.8%
	Obesity	Yes	1.38 (1.03, 1.86)	0.03	35.3%
		No	ref		25.9%
	Type II Diabetes	Yes	1.54 (1.05, 2.25)	0.03	37.4%
		No	ref		28.9%
HCC	Age at Start of Clinical Follow-up	<30	0.0	<0.0001	0.0%
		30–39	0.04 (0.01, 0.14)		2.9%
		40–49	0.25 (0.12, 0.52)		9.9%
		50+	ref		24.3%
	HCV Genotype	1	ref	0.002	6.8%
		2	0.59 (0.17, 1.99)		4.6%
		3	3.06 (1.43, 6.55)		8.8%
	Sex	M	3.63 (1.60, 8.23)	0.006	10.9%
		F	ref		3.3%
Liver Related Death and Liver Transplant [a]	Age at Start of Clinical Follow-up	<30	0.03 (0.01, 0.13)	<0.0001	4.5%

Outcome	Risk Factor	Level	Hazard Ratio	P-value	Proportion who have had Outcome at 15 Years of Clinical Follow-up
		30–39	0.16 (0.09, 0.28)		9.0%
		40–49	0.29 (0.17, 0.49)		16.5%
		50+	ref		27.9%
	HCV Genotype	1	ref	0.001	11.4%
		2	1.20 (0.70, 2.07)		13.4%
		3	2.42 (1.48, 3.98)		22.9%
	Heavy ETOH	Yes	2.87 (1.81, 4.55)	<0.0001	23.1%
		No	ref		11.6%

[a]Type II diabetes p-value 0f 0.06 with a hazard ratio of 1.65 in this model.