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Liver Fibrosis Progression among Persons with Recently Acquired HCV Infection

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Background

- Hepatitis C virus infection (HCV) is a slowly progressive chronic disease. Many HCV infected patients do not develop liver-related complications even after many years of infection.
- Since the most severe consequences of chronic HCV infection are due to liver disease, it is important to define the rate of progression of liver fibrosis and hepatic decompensation, and the potential mediators of these consequences.
- Studying clinical consequences of HCV infection is often limited by the lack of knowledge of actual time of infection. Our understanding of the natural history of HCV infection has been gained from small studies of single source outbreaks or among high risk target populations.
- To understand the true nature of the course of HCV infection and clinical consequences arising from it, a relatively precise estimate of the time of infection with adequate follow up time in a national, geographically diverse sample and appropriate HCV uninfected controls is needed.

Objectives

- To determine the rate of fibrosis progression in HCV infected persons with a relatively well defined time of infection compared with HCV uninfected controls
- To determine the time to development of cirrhosis in HCV infected persons compared with HCV uninfected controls
- To determine the factors associated with fibrosis progression and liver cirrhosis in these persons

Methods

We used the third iteration of the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES 3.0) to identify newly diagnosed HCV infected subjects and HCV uninfected controls between October 1, 2001 and September 30, 2012.

We identified subjects who were HCV antibody negative upon first testing, but had a subsequent positive HCV antibody test. The actual time of infection was assigned to be the mid-point between the negative and positive test.

We excluded subjects with HIV infection, those with no labs available to calculate baseline APRI scores and those who received any treatment for HCV, those with < 24 months of follow up after baseline, and those with hepatitis B surface antigen positivity.

Controls were identified based on a negative HCV antibody test in the same year as first positive for HCV infected persons, and matched 1:1 on age (5-year blocks), race and sex.

Comorbid medical and psychiatric diagnoses and history of alcohol and drug abuse diagnoses were based on laboratory values or presence of at least one inpatient or two outpatient ICD-9 codes.

Diabetes was defined by a combination of laboratory values, ICD-9 codes and hypoglycemic medications as per our previously published criteria.{1689} Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 as calculated by the simplified Modification of Diet in Renal Disease (MDRD) equation.{1822} Hepatic decompensation was defined as a primary hospital discharge diagnosis or two or more outpatient diagnoses for ascites, spontaneous bacterial peritonitis, or esophageal variceal hemorrhage.{1971} Anemia was defined as hemoglobin of <13g/dl for men and <12g/dl for women.

APRI was chosen as measures of fibrosis progression based on previously published data suggesting its utility to detect liver involvement in HCV infected persons, and was computed at 6-monthly intervals as follows:

APRI: (AST/upper limit of normal considered here as 40 IU/L)/platelet count (platelets × 10^9/L) × 100

Analysis

Three groups were compared: HCV RNA+; HCV RNA-; HCV uninfected

Factors associated with development of cirrhosis or hepatic decompensation were determined using Cox regression analysis. Kaplan-Meier plots were generated to show and compare liver fibrosis progression over time.

Results

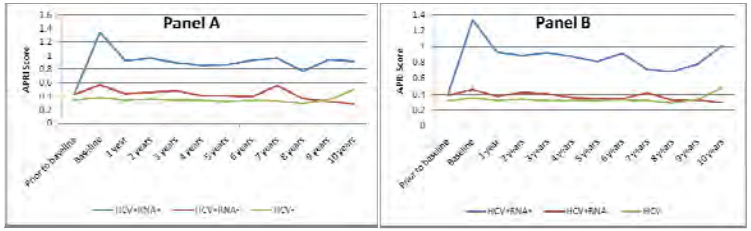
Table 1. Baseline characteristics of subjects by HCV infection category.

	HCV Ab+ RNA+(N=1182)	HCV Ab+ RNA-(N=902)	HCV Ab-(N=2084)	P-value
Age	50.05+-11.2	55.6+11.22	53+-9.94	<.0001
Race				0.2359
White	64.72%	66.96%	65.69%	
Black	23.35%	19.29%	21.59%	
Hispanic	5.84%	5.43%	5.66%	
Other	6.09%	8.31%	7.05%	
Sex (Male)	93.32%	92.57%	92.99%	0.8045
Body mass index, Mean+/- SD, kg/m^2	27.37+/-7.75	29.4+/-8.41	29.64+/-6.14	<.0001
Comorbidities				
Diabetes	19.63%	24.61%	18.67%	0.0008
Hypertension	44.08%	53.77%	44.63%	<.0001
Chronic kidney disease, stage 3-5	8.29%	11.86%	6.62%	<.0001
Chronic obstructive pulmonary disease	12.61%	14.75%	7.87%	<.0001
Cardiovascular disease	9.90%	11.53%	7.49%	0.0009
Alcohol abuse or dependence	45.26%	28.71%	16.41%	<.0001
Drug abuse or dependence	51.78%	25.17%	12.62%	<.0001
Significant fibrosis: APRI>1.5	24.28%	4.66%	1.97%	<.0001
Cirrhosis: APRI>2.0	16.5%	3.7%	1.5%	<0.001
Hepatic decompensation	0.85%	0.89%	0.24%	0.0247
Anemia	22.59%	27.16%	16.36%	<.0001
Labs				
AST	114.14+-156.62	44.21+-102.68	34.54+-68.18	<.0001
ALT	164.04+-232.66	47.23+-114.47	40.38+-70.89	<.0001
APRI	1.34+-1.99	0.57+-1.65	0.41+-1.11	<.0001
Hemoglobin, mean, SD (g/dl)	14.65+-1.71	14.25+-1.83	14.58+-1.67	<.0001

Table 2. Factors associated with progression to a diagnosis of cirrhosis (Multivariable Cox regression, HR(95% CI)

	HCV Ab+ RNA+(N=1182)		HCV Ab+ RNA-(N=902)		HCV Ab-(N=2084)	
Demographics	HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P
Age, per 10 year increase	1.10(0.98, 1.24)	0.1	1.10(0.83, 1.45)	0.52	0.87(0.61, 1.23)	0.43
Race(White vs. non-White)	1.36(1.07, 1.73)	0.01	1.10(0.65, 1.87)	0.72	1.91(0.93, 3.95)	0.08
Sex(Male)	1.61(0.92, 2.83)	0.1	1.40(0.43, 4.58)	0.58	0.51(0.17, 1.48)	0.21
Body mass index, <30 vs. ≥30	1.15(0.89, 1.48)	0.3	1.11(0.65, 1.90)	0.72	0.96(0.50, 1.86)	0.9
Comorbidities						
Diabetes	1.60(1.21, 2.11)	<0.001	1.41(0.81, 2.46)	0.23	1.12(0.50, 2.50)	0.78
Hypertension	1.16(0.90, 1.48)	0.26	1.15(0.66, 2.00)	0.63	1.60(0.81, 3.17)	0.17
CKD stage 3-5	1.22(0.82, 1.83)	0.33	0.46(0.16, 1.32)	0.15	0.68(0.15, 3.01)	0.61
COPD	0.92(0.66, 1.29)	0.64	1.03(0.54, 1.97)	0.92	0.54(0.16, 1.79)	0.31
CVD	0.83(0.56, 1.23)	0.35	1.17(0.54, 2.50)	0.69	0.94(0.27, 3.30)	0.92
Alcohol abuse or dependence	2.01(1.53, 2.63)	<.0001	5.51(3.08, 9.83)	<.0001	7.16(3.49, 14.68)	<.0001
Drug abuse or dependence	0.75(0.57, 0.99)	0.04	0.64(0.36, 1.17)	0.15	0.33(0.12, 0.93)	0.04
Anemia	0.97(0.74, 1.28)	0.84	1.83(1.07, 3.13)	0.03	1.79(0.83, 3.90)	0.14

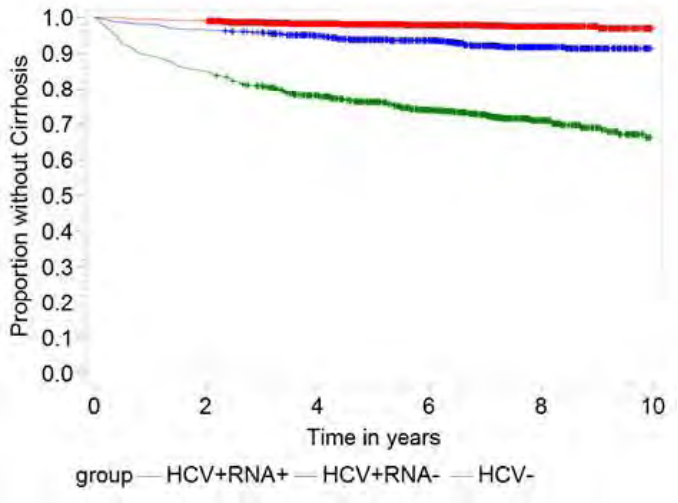
Figure 1. Progression of liver fibrosis over time using APRI as measures of liver fibrosis.
Panel A represents all subjects; Panel B excludes subjects with a diagnosis of alcohol abuse or dependence



Baseline defined as first HCV+ date for cases and HCV- date for controls.
APRI "Prior to baseline" is the average of 3 values closest to baseline prior to the baseline value.

Results

Figure 2. Kaplan-Meier curves demonstrating time to development of cirrhosis. (P<0.0001 for each comparison). (Cirrhosis defined as APRI>2.0)



Conclusions

- In persons with newly diagnosed HCV infection, progression of fibrosis as measured by APRI is slow over the first 10 years.
- Persons with HCV viremia have the highest risk of progression; however, HCV infected persons who have no detectable viremia are also at a higher risk compared with HCV uninfected persons.
- Alcohol abuse or dependence is the only consistent factor associated with development of cirrhosis in all groups, though this association is of lower magnitude in those with HCV viremia. Diabetes is associated with a higher risk for cirrhosis in HCV infected persons with viremia, but not in those without viremia or HCV uninfected controls.
- Persons with HCV viremia have a substantially higher risk of developing cirrhosis, although those with no viremia are also at a higher risk when compared with HCV uninfected persons.

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