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The Effects of Alcohol on Spontaneous Clearance of Acute Hepatitis C Virus Infection in Females versus Males

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Abstract

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Conflicts of Interest
The authors declare that there are no conflicts of interest.

Background—Approximately one quarter of persons exposed to hepatitis C virus (HCV) will spontaneously clear infection. We undertook this study to investigate the impact of alcohol on likelihood of HCV spontaneous viral clearance stratified by sex groups.

Methods—Pooled data from an international collaboration of prospective observational studies of incident HIV and HCV infection in high-risk cohorts (the InC3 Study) was restricted to 411 persons (or 560.7 person-years of observation) with documented acute HCV infection and data regarding alcohol use. The predictor of interest was self-reported alcohol use at or after estimated date of incident HCV infection and the outcome was HCV spontaneous clearance. Sex stratified Cox proportional hazards models were used to evaluate the association between alcohol and spontaneous clearance, adjusting for age, race/ethnicity, and *IFNL4* genotype.

Results—The median age was 28.5 years, 30.4% were women, 87.2% were white, and 71.8% reported alcohol use at or after incident infection. There were 89 (21.6%) cases of spontaneous clearance observed, 39 (31.2%) among women and 50 (17.5%) in men ($p<0.01$). Overall, spontaneous clearance occurred less frequently among participants who drank alcohol compared to those who did not drink (18.9% v. 28.5%, $p=0.03$). After adjustment for other covariates, alcohol was significantly and independently associated with lower relative hazards for spontaneous clearance of HCV in women (AHR=0.35; 95% CI: 0.19-0.66; $p=0.001$) but not in men (AHR=0.63; 95% CI: 0.36-1.09; $p=0.10$).

Conclusion—Results indicate that abstaining from drinking alcohol may increase the likelihood of spontaneous clearance among women.

Keywords

Ethanol; substance use; injection drug use; sexual dimorphism; hepatitis c virus; blood-borne viral infections

1. INTRODUCTION

Hepatitis C virus (HCV) infection is conservatively estimated to affect 1% of the world's population (Gower et al., 2014) and continues to be a global health issue primarily associated with unsafe parenteral injections and injection drug use (Nelson et al., 2011). Effective treatments are available, yet are extremely costly, and many barriers to uptake remain, particularly among people who inject drugs (PWID; Bruggmann, 2012). Approximately 25% of persons exposed to HCV will spontaneously clear the infection without treatment (Micallef et al., 2006; Page et al., 2009). Understanding the mechanisms underlying clearance can inform strategies to control HCV.

To date, a number of factors have been found to impact HCV spontaneous clearance. CD4+ and CD8+ T-cell responses enhance HCV clearance (Cox et al., 2005; Shoukry et al., 2003), and females are more likely to clear HCV than males (Page et al., 2009), especially if they are homozygous for the C allele of the single nucleotide polymorphism (SNP) rs12979860 (Grebely et al., 2014), which is located within intron 1 of the interferon lambda 4 (*IFNL4*) gene (Prokunina-Olsson et al., 2013). The impact that behavioral exposures, including the effects of alcohol, have on HCV spontaneous clearance is less well studied. In vitro, alcohol increases HCV replication in some models through modulation of interferon signaling

pathways and microRNA expression (Bukong et al., 2013; Osna et al., 2015; Ye et al., 2010). Alcohol has been shown to impair adaptive immune responses that are essential for eliminating HCV, including the altering of antigen presentation on immune cells (Osna, 2009; Osna et al., 2009), interfering with key proteasomes involved with degradation of HCV (Osna et al., 2014), and enhancing the effects of HCV on dendritic cell function (Szabo et al., 2006), Prevalence of concurrent alcohol use is high among PWID: one study of young adult injectors found that 68% reported current alcohol use meeting or exceeding cutoffs for hazardous use (Le Marchand et al., 2013).

Observational studies that have examined the impact of alcohol on HCV clearance have shown mixed results. In a large cross-sectional study of HCV-seropositive veterans, individuals with a clinical diagnosis of an alcohol use disorder were half as likely to have an undetectable viral load indicating prior spontaneous clearance (Piasecki et al., 2004). However, two community-based studies did not find significant associations between any alcohol use and HCV clearance (Grebely et al., 2007; Shah et al., 2012). To date, no studies of acute HCV infection have prospectively ascertained the impact of alcohol use on HCV viral clearance or the effect of alcohol on HCV clearance separately among females versus males. Men are more likely to drink alcohol and drink in larger amounts; however, women absorb alcohol more quickly and take longer to metabolize it (Center for Disease Control and Prevention, 2014). Patterns of alcohol consumption have been shown to have differential effects on markers of liver damage in women, compared to men (Stranges et al., 2004), and alcohol has been shown to be associated with more advanced fibrosis at lower levels of intake among women compared to men (Hezode et al., 2003). Furthermore, alcohol use can potentially impact sex hormone levels (Gill, 2000), which have been shown to be important mediators of immune responses to infectious diseases (Bouman et al., 2005).

This study examined the impact of drinking alcohol on likelihood of HCV spontaneous clearance in a large sample of merged cohorts of persons with documented acute HCV who were prospectively followed over time with repeated measures of HCV viral load and drinking self-report. In addition, we assessed whether associations between alcohol and spontaneous clearance differed among women compared to men.

2. MATERIAL AND METHODS

2.1 Study Design and Population

The InC3 study, a collaboration of nine prospective cohorts in the United States, Australia, Canada, and The Netherlands, evaluates HCV and HIV outcomes among people at high risk of HCV, the majority of who have a history of injection drug use, and has been previously described in detail (Grebely et al., 2013). Participants were recruited and prospectively followed between 1979 and 2012. For the current study, only individuals from longitudinal cohorts with documented acute HCV and data on alcohol use are included. Acute HCV was defined as either: 1) HCV seroconversion with an anti-HCV negative test followed by either an anti-HCV positive or HCV RNA-positive test within two years or 2) documented symptomatic HCV infection, defined by a positive anti-HCV/ HCV RNA test, jaundice or alanine aminotransferase (ALT) elevation >400 U/L, or history of high-risk exposure within three months of clinical manifestation of acute HCV. Individuals treated for HCV within 26

weeks of incident HCV were excluded, as they were treated within the acute window during which spontaneous clearance could occur.

2.2 Study Procedures and Laboratory Testing

The data collected at each site every one to six months included baseline and longitudinal information on socio-demographic and exposure variables (such as date of birth, sex, ethnicity, housing, parenteral/injecting, and sexual exposures) and HCV testing (anti-HCV and HCV RNA testing). The choice of qualitative and quantitative HCV RNA testing varied by cohort but was consistent at each site. Qualitative HCV RNA testing was performed using the following assays: Versant TMA (<10 IU/mL; Bayer, Pymble, New South Wales, Australia), COBAS AmpliPrep/COBAS Taq-Man (<15 IU/mL; Roche, Branxhburg, NJ), COBAS Aplicore HCV Test (v2.0; <50 IU/mL: Roche Diagnostics, Mannheim, Germany), or discriminatory HCV transcription-mediated amplification component of the Procleix HIV-1/HCV (<12 copies/mL; Gen-Probe, San Diego, CA). Quantitative HCV RNA testing was performed using the Versant HCV RNA 3.0 (<615 IU/mL: Bayer), Cobas Amplicor HCV Monitor (version 2.0; <600 IU/mL; Roche), or an in-house polymerase chain reaction (<1,000 IU/mL). HCV genotype was determined by line-probe assay (Versant LiPa1/LiPa2; Bayer) or HCV sequencing at acute HCV detection. Among those with undetectable HCV RNA and available samples, Murex HCV serotyping was performed to determine HCV genotype (Murex Biotech Limited, Dartford, UD). *IFNL4* genotype was determined by sequencing of the RS12979860 single-nucleotide polymorphism, as previously described (Grebely et al., 2014). The total number of participants, those lost to follow-up, and the number defined as having HCV acute infection by different methods and spontaneous clearance outcomes are presented in Figure 1. All participants provided written informed consent, and cohort protocols were approved by local ethics committees. Approval was also obtained for the merged dataset, which contained no identifiers.

2.3 Study Measures

2.3.1 Outcomes—Spontaneous clearance was defined by two consecutive undetectable HCV RNA test results greater than or equal to four weeks apart after date of acute infection. The methods for estimating the date of infection have been previously described (Grebely et al., 2014). Briefly, the date of HCV infection was estimated as either: (1) the midpoint between last negative and first positive anti-HCV test for those whose new infection was identified via anti-HCV seroconversion or (2) the date of first HCV RNA positive visit minus 28 days for those whose new infection was identified via a RNA positive/anti-HCV negative test. The estimated date of clearance was defined as the midpoint between the first of two consecutive undetectable qualitative HCV RNA tests and the last sample with detectable HCV RNA (or the estimated date of infection, in the event that the sample collected at the time of acute detection was HCV RNA undetectable). Time to clearance was calculated as the time from the estimated date of infection to the estimated date of clearance. For those without clearance, follow-up time was calculated from the estimated date of infection until the date of the last therapy-naïve detectable HCV RNA test. For participants with only one undetectable HCV RNA as their last measurement, follow-up time was calculated from the estimated date of infection until the date of the last positive HCV RNA test. Participants treated for HCV were censored at the date of treatment initiation.

2.3.2 Predictors—The main exposure of interest was participant self-report of alcohol use at or any time after the estimated date of HCV acute infection. The length of the intervals for assessments for alcohol use among the cohorts varied from three to six months across the cohorts. Alcohol use was defined as any self-reported use (yes/no) within the follow-up period from HCV acute infection to spontaneous clearance or censorship. Post-hoc analyses were performed on a smaller sub-set of the sample with a 3-level variable for alcohol use (daily use, non-daily use, no use). This data was not available for all cohorts, as questions on alcohol use varied across cohorts. As per study guidelines, the InC3 data-coordinating center reviewed all questions and then consolidated the questions and responses in a manner that allowed data to be combined while maintaining the integrity of the responses. Alcohol in binary form (non-drinkers vs. drinkers) and ordinal form (non-drinkers, less than daily drinkers, and daily drinkers) were the two variables that were constructed. The alcohol variable in its ordinal form had more missing than alcohol in binary form, as it was not available for several cohorts. Additional covariates that were selected to be included in the analysis a priori included: age, race/ethnicity, and *IFNL4* genotype (SNP rs12979860; CC versus CT/TT). Sex was considered to be a potential effect-modifier, and therefore, results were stratified based on sex.

2.4 Statistical Analyses

Descriptive analyses compared characteristics of subjects with and without alcohol use. The effects of alcohol use on time to HCV clearance were assessed by Kaplan-Meier analyses with significance assessed by log-rank test. Survival time was defined as time from acute infection to date of spontaneous clearance. Subjects entered into the analysis at the date of acute infection and remained until date of spontaneous clearance, or they were censored at the date of the last therapy-naïve detectable HCV RNA test. Patients who died or were lost to follow-up were censored at their last visit. Cox proportional hazards analysis were used to assess the independent effects of alcohol, adjusting for age, race/ethnicity, site, and *IFNL4* status on HCV spontaneous clearance. Alcohol use was treated as a time-invariate variable in the analyses. To assess the effects of sex, we included an interaction term between sex and alcohol use and estimated both male- and female-specific adjusted hazard ratios using the post-model linear combination of the coefficients. The test for interaction was done using a Wald test for the interaction term included in the fitted model. Adjusted hazard ratios (AHR) and 95% confidence intervals (CI) are reported. Sensitivity analyses were conducted adjusting for current frequency of injection drug use (none versus weekly, several times a week, and daily) and HCV genotype for subjects with available data. Cox models were checked for violation of the proportional hazards assumption by assessing scaled Schoenfeld residuals and log-minus-log survival plots for patterns of non-proportionality. All analyses were performed using Stata statistical software (v13.0; StatCorp LP, College Station, TX).

3. RESULTS

The sample was comprised of 411 participants with documented acute HCV and data on concomitant alcohol use. The median age (interquartile range [IQR]) was 28.5 years (23.8, 36.5); 125 (30.4%) were women, 354 (87.2%) were Caucasian, and 295 (71.8%) reported

alcohol use at or after acute infection. There were no significant differences in alcohol use by age, race/ethnicity, HCV genotype, or *IFNL4* genotype (Table 1).

There were 89 (21.6% of 411 individuals) cases of spontaneous clearance, 39 (31.2%) among women and 50 (17.5%) in men. Overall, spontaneous clearance risk was less common among participants who drank alcohol compared to those who did not drink alcohol (56/295 = 18.9% v. 33/116 = 28.5%, p=0.03). The total follow-up time was 560.7 person-years of observation (pyo). Table 2 presents rates of spontaneous clearance overall by drinking status and stratified by sex. Female participants who did not drink alcohol had the highest rate (40.1/100 pyo) of spontaneous clearance.

The Kaplan Meier curves of time to HCV clearance (shown as proportion with HCV persistence) are presented in Figure 2. Non-drinking females demonstrated the highest rate of spontaneous clearance (group D) compared to others. In the unadjusted Cox proportional hazards analyses, alcohol use relative to no alcohol use was significantly associated with lower hazards for spontaneous clearance of HCV in women (HR=0.43; 95% CI: 0.22-0.84; p=0.01) but not in men (HR=0.84; 95% CI: 0.65-1.08; p=0.18). After adjustment for age, race/ethnicity and *IFNL4* genotype, alcohol use remained significantly associated with lower hazards for spontaneous clearance of HCV in women (AHR=0.35; 95% CI: 0.19-0.66; p=0.001) compared to men (AHR=0.63; 95% CI: 0.36-1.09; p=0.10) (Figure 3). The test of homogeneity for gender for the effect of alcohol on HCV clearance (i.e., test for interaction) was statistically significant (χ^2= 27.3, p<0.001). Sensitivity analyses adjusting for frequency of injection drug use and for HCV genotype did not substantively change results. After adjustment for HCV genotype and injecting frequency, alcohol was still independently associated with a lower hazard for spontaneous clearance of HCV in women (AHR=0.33; 95% CI: 0.14-0.78; p=0.01) and the association between alcohol use and rate of spontaneous clearance became stronger among the men, but did not reach statistical significance (AHR=0.51; 95% CI: 0.26-1.02; p=0.06).

When exploring post-hoc analyses with the ordinal three-level alcohol variable, the total sample size was reduced to 270 participants with only 63 demonstrating spontaneous clearance (Table 3). The crude HR for the less than daily drinkers was 0.90 (P=0.211), while for the daily drinkers it was estimated as 0.63 and statistically significant (P=0.023). Due to small sample size and lack of power, we were not able to do stratified Cox models by sex or further adjust for other covariates.

4. Discussion

This study of persons with acute HCV who were followed prospectively found that alcohol use was associated with decreased relative hazards for spontaneous clearance of HCV; sex-stratified analyses demonstrated that there was a stronger, and significant, effect in women compared to men. These results add to the existing body of literature that demonstrates the adverse impact of drinking alcohol on HCV-related outcomes. In addition to contributing to increased risk for cirrhosis (Corrao and Arico, 1998; Hutchinson et al., 2005) and hepatocellular carcinoma (Donato et al., 2002), it appears that drinking alcohol increases the

likelihood that an acute HCV infection will not resolve but lead to chronic infection in women.

These results also support and are consistent with prior experimental research demonstrating that alcohol has an impact on innate and adaptive immune processes that are critical for spontaneous resolution of HCV infection. Ethanol has been shown to impact immune responses to HCV structural and non-structural proteins and impairs dendritic cell responses (Osna et al., 2014; Szabo et al., 2006) and can impair proteosomic activity that is necessary for the degradation of HCV proteins leading to an effective cellular immune responses (Osna et al., 2014). The results of this study are relatively consistent with results from a prior cross-sectional study that reported that those with a prior diagnosis of an alcohol use disorder were half as likely to have evidence of spontaneous clearance (i.e., HCV seropositive with an undetectable HCV viral load; Piasecki et al., 2004). However, as far as we are aware, this is the first study to date that has prospectively examined the impact of alcohol on spontaneous clearance among persons with documented acute infection.

The results of the sex-stratified analyses showing differences in clearance in association with alcohol exposure between females and males adds to increasing evidence of sexual dimorphism and HCV outcomes (Grebely et al., 2014; Page et al., 2009). These results should be confirmed in other samples; however, they are consistent with the emerging paradigm of sex-based differences in HCV immune responses that lead to clearance. In general, women have been noted to have a lower burden of infectious disease but a higher burden of autoimmune disease (Bouman et al., 2005) and an increased magnitude of immune and inflammatory responses compared to men (Klein et al., 2010). One hypothesis is that there may be sex-hormone-specific receptors for many of the immune pathways responsible for HCV natural history. Animal studies have demonstrated estrogen effects hepatic stellate cells that contribute to fibrosis (Shimizu et al., 1999), and human studies have also documented lower rates of fibrosis associated with higher estrogen states (Di Martino et al., 2004; Villa et al., 2012). However, it is also possible that the gender-related differences in spontaneous clearance that we observed could be related to unmeasured differences in the patterns of drinking and/or alcohol exposure among women compared to men. More research is needed to understand the immunological basis for these sex-specific effects in order to generate a broader understanding of the range of human immune responses to viral infections.

These results contribute to a growing body of evidence indicating the harmful effects of alcohol. Among PWID, risky alcohol use has also been shown to be associated with HIV risk behaviors (Le Marchand et al., 2013; Stein et al., 2002) and mortality (Johnson et al., 2015). Findings provide additional motivation for providers to screen and address alcohol use among persons who are at high risk of HCV, including PWID. Providers who care for PWID, especially young adults who are not yet infected with HCV, may wish to counsel them that concurrent alcohol use may increase their likelihood of developing a chronic infection with HCV should they become exposed.

There were limitations to this study. Cohorts of participants with acute HCV were combined to provide data, and as such, there was some heterogeneity of measurement (e.g., HCV RNA

assays differed across cohorts). Adjusting for site was one strategy to control for potential unmeasured confounding between sites. Another limitation was the limited number of participants who had data on alcohol use relative to overall Inc3 study sample, as presented in Figure 1. Information about the frequency of alcohol used by participants was not available for the full sample of participants in all cohorts. Exploratory analyses demonstrated few outcomes in each category of responses when stratified by gender, so we chose to use a dichotomous variable for alcohol consumption for our main analysis. As such, we are unable to assess whether there is a specific threshold or dose effect of alcohol on spontaneous clearance or whether there is a dose-response relationship between alcohol use and the odds of clearance. However, we performed post-hoc analyses on a smaller subset of our sample who had data on daily use v. non-daily use (v. no use). Those results were limited by small numbers in the non-daily use category, but they did not support the same association between non-daily drinkers. Also, our study did not assess chronic alcohol consumption; other research has shown the effects of acute alcohol consumption on viral replication differ from those of chronic alcohol consumption (McCartney and Beard, 2010). Alcohol use was based on self-report and, thus, could be subject to social desirability bias. However, prior research has demonstrated there is little bias on self-report of alcohol use in this population with objective measures (Jain et al., 2014). Finally, although this study represents a relatively large sample of patients with acute HCV who were prospectively followed, the absolute number of outcomes of spontaneous clearance is modest. As such, our sex-specific results should be interpreted cautiously and results should be confirmed in other samples. In addition, the relatively small percentage of non-whites represented is a study limitation.

In summary, this prospective study of HCV clearance among people with acute infection found that self-reported alcohol use was associated with a lower relative hazard of spontaneous clearance, and sex-stratified analyses suggested strong and significant associations among women only. These results underscore the adverse effects of alcohol use on the natural history of HCV disease and provide additional evidence of sexual dimorphism in HCV outcomes.

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Highlights

- The study included data from prospective cohorts of substance users with acute HCV.
- Rates of spontaneous clearance of HCV were higher among those who did not drink alcohol.
- A stronger, significant effect of alcohol use was found for women compared to men.

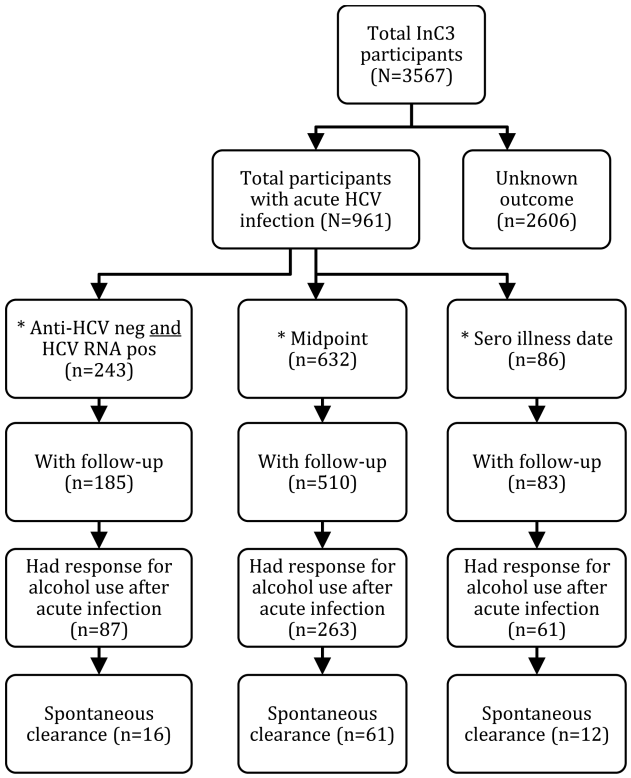
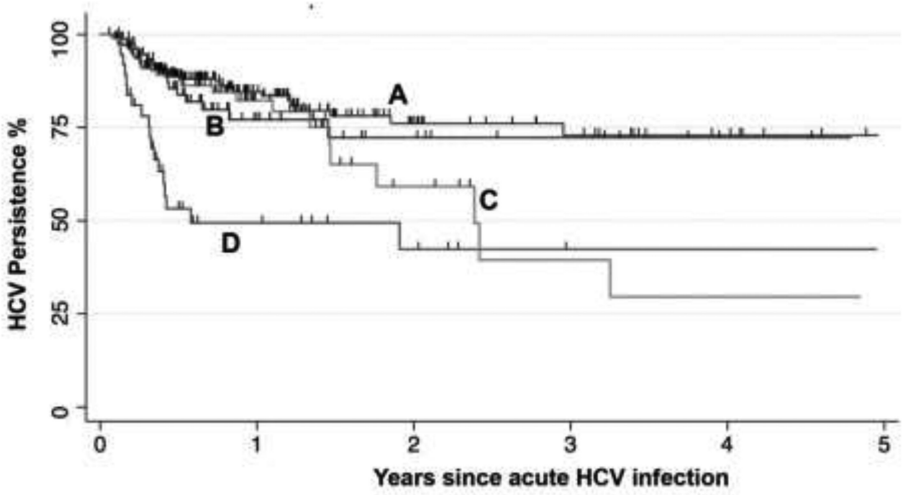


Figure 1.

The overview of InC3 participants and their spontaneous clearance outcome.

*Method for defining date of acute HCV infection



Number at risk						
A. Drinker, Males	207	80	34	23	15	9
B. Non-drinker, Males	78	25	12	8	4	3
C. Drinker, Females	88	29	9	4	3	3
D. Non-drinker, Females	37	11	6	2	2	2

Figure 2.

Kaplan Meier curves of HCV persistence by sex and alcohol-drinking status at or after HCV acute infection.

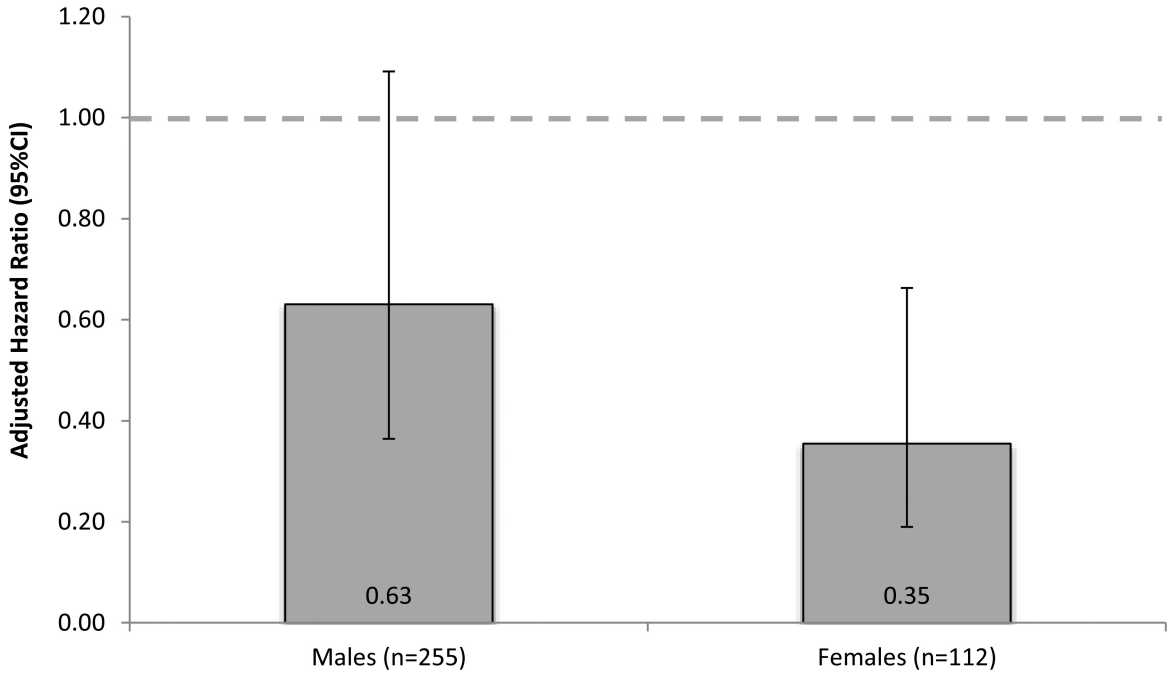


Figure 3.

Adjusted* relative hazards for spontaneous clearance associated with drinking alcohol in females versus males.

*Models adjusted for age, race/ethnicity, IFNL4, and study site.

Table 1

Characteristics of participants by alcohol drinking status concurrent with acute HCV infection

Characteristics	Overall (n=411)	No Alcohol (n=116)	Any Alcohol (n=295)	P-value
Age at infection*, Median (IQR)	28.5 (23.8, 36.5)	29.6 (24.8, 38.4)	28.2 (23.5, 35.2)	0.07
Female*	30.4%	31.9%	29.8%	0.25
Race/ethnicity (n=406)				
Caucasian	87.2%	87.0%	87.3%	
Hispanic/Latino	3.2%	2.6%	3.4%	
Asian	3.2%	3.5%	3.1%	0.69
Indigenous	2.7%	1.7%	3.1%	
Black	0.7%	1.7%	0.3%	
Other	3.0%	3.5%	2.8%	
Any history of drug injection	94.4%	93.9%	94.6%	0.81
IFNL4 (n=372)				
TT	11.3%	11.1%	11.4%	0.60
CT	38.7%	42.6%	37.1%	
CC	50.0%	46.3%	51.5%	
Genotype (n=340)				
One	48.3%	51.1%	47.1%	0.52
Non-one	51.7%	48.9%	52.9%	
Recruitment sites/Cohort name*				
Amsterdam/ACS	9.3%	17.2%	6.1%	
Sydney/AUS	32.1%	37.1%	30.2%	
Montreal/HEP	24.1%	21.6%	25.1%	0.001
Sydney/HITC	4.4%	1.6%	5.3%	
Melbourne/NET	2.6%	3.5%	2.4%	
San Francisco/UFO	27.5%	19.0%	30.9%	

*No missing data.

Table 2

Rates of spontaneous clearance of HCV infection (per 100 person-years observation) among drinkers and non-drinkers of alcohol, stratified by sex.

Subgroup	Drinking status	N	SC cases	pyo	Incidence/100 pyo (95% CI)	RR (95% CI)	P-value
Overall							
	Non-drinkers	116	33	153.5	21.5 (15.3, 30.2)	1.0	0.04
	Drinkers*	295	56	407.2	13.8 (10.6, 17.9)	0.6 (0.4, 0.9)	
Males							
	Non-drinkers	79	15	108.1	13.9 (8.4, 23.0)	1.0	0.69
	Drinkers	207	35	284.3	12.3 (8.8, 17.1)	0.9 (0.5, 1.6)	
Females							
	Non-drinkers	37	18	44.8	40.1 (25.3, 63.7)	1.0	0.007
	Drinkers	88	21	123.0	17.1 (11.1, 26.2)	0.4 (0.2, 0.8)	

SC: Spontaneous Clearance; RR: Rate Ratios calculated with the Mantel-Haenszel method; PYO: Person-years of observations; CI: Confidence Interval.

*Alcohol drinking status at or after acute HCV infection.

Table 3

Rates of spontaneous clearance of HCV infection (per 100 person-years observation) among daily drinkers, non-daily drinkers and non-drinkers of alcohol, stratified by sex.

Subgroup	Drinking status	SC cases	pyo	Incidence/100 pyo (95% CI)	RR (95% CI)	P-value
Overall						
	Non-drinkers	42	225.3	18.6 (13.8, 25.2)	1	
	Less than daily drinkers	12	62	19.3 (11.0, 34.1)	1.04 (0.54, 1.97)	0.91
	Daily drinkers	9	156.9	5.7 (3.0, 11.0)	0.3 0.15, 0.63	0.0007
Males						
	Non-drinkers	19	155.2	12.2 (7.8, 19.2)	1	
	Less than daily drinkers	9	53.2	16.9 (8.8, 32.5)	1.3 0.63, 3.06	0.42
	Daily drinkers	5	105.2	4.8 (2.0, 11.4)	0.4 0.14, 1.04	0.06
Females						
	Non-drinkers	23	69.6	33.1 (22.0, 49.7)	1	
	Less than daily drinkers	3	8.9	33.9 (10.9, 105.0)	1.0 0.31, 3.41	0.97
	Daily drinkers	4	51.7	7.7 (2.9, 20.6)	0.2 0.08, 0.68	0.003

SC: Spontaneous Clearance; RR: Rate Ratios calculated with the Mantel-Haenszel method; PYO: Person-years of observation; CI: Confidence Interval.

*Alcohol drinking status at or after acute HCV infection.