Differences in sustained virologic response to direct-acting antiviral therapy for chronic hepatitis C by sex – results from the CanHepC retrospective registry

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CanHepC
Canadian Network on Hepatitis C
Réseau Canadien sur l'Hépatite C

Background

- There has been variable evidence to suggest that biologic sex may act as an independent predictor of sustained virologic response (SVR) to direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV).
- In 2016, a large real-world effectiveness study of all-oral HCV antiviral therapies comprised of over 12,000 patients with genotype 1 demonstrated that females had a greater odds of achieving SVR over males[1].
- Similar findings were reported in a study of patients with advanced fibrosis being treated with sofosbuvir-based regimens[2].
- Conversely, a recently published study by Kouris et al. involving only genotype 1 HCV patients failed to replicate these findings[3].
- Overall, limited studies specifically focused on DAAs and biologic sex appear to have been published thus far.

The Canadian Network on Hepatitis C (CanHepC) retrospective registry project has combined pre-existing demographic and outcome data on patients with chronic HCV who were assessed at 10 academic and community sites across Canada (Figure 1). Understanding biologic sex-specific differences related to HCV acquisition and treatment outcomes is essential to inform optimal care models.

Study aim: To assess demographic and treatment outcomes by biologic sex for persons treated with DAA interferon-free therapies in this cohort.

Figure 1: Geographic distribution of sites

Methods

- Individuals included in the cohort who had data available on biologic sex, type of HCV treatment received and SVR were included in the final analysis (N=1,008/2,658).
- Basic means and proportions were calculated to identify crude differences between males and females treated with DAAs. Only variables at least 50% of the data available were analyzed.
- Odds ratios were calculated for the relationship between biologic sex and SVR using forward stepwise logistic regression including variables found to suggest possible association in univariate analysis (p<0.10) to both the exposure (biologic sex) and outcome (SVR).
- Likelihood ratio (LR) tests will be used to determine whether possible confounders should be included in the final model.

Results

- Baseline characteristics (Table 1) differed significantly only with regard to reported injection drug use (IDU); however, data were missing on 40.6% of all included individuals.
- Overall SVR among males was 93.5% (95% CI 91.6%-95.3%) versus 98.13% (95% CI 96.6%-99.6%) among females. No difference was found between genotypes (Figure 2). Differences were found specifically in the 60+ year age groups (Figures 3 & 4).
- The proportion of those achieving SVR (Table 2) was found not to be significantly different at baseline for mean age, non-genotype 1 infection, distribution of Metavir scores or HIV infection.
- Possible confounding factors (HIV status and IDU) were tested in a multivariable model. Neither HIV (LR p=0.406) nor IDU (LR p=0.348) were found to significantly improve the model.
- **Overall, females were statistically more likely to achieve SVR when compared to males (OR 3.68, 95% CI 1.55-8.72, p=0.003).**

Table 1: Baseline characteristics of DAA-treated participants with SVR and biologic sex information available

	Male (n=687)	Female (n=321)	p-value
Mean age, years (95% CI)	54.08 (53.27-54.88)	53.83 (52.50-55.16)	0.744
HIV, % (n)	5.86 (36)	3.09 (9)	0.073
Injection drug use[1], % (n)			
Yes (Current/Past)	56.59 (236)	36.26 (66)	<0.001
Never	43.41 (181)	63.74 (116)	
Non genotype 1, % (n)	23.09 (157)	22.40 (71)	0.809
Metavir Score, % (n)			
F0-F1	30.53 (174)	34.59 (92)	0.448
F2-F3	33.86 (193)	30.45 (81)	
F4	35.61 (203)	34.96 (93)	

[1] Data on injection drug use status was only available for 59.4% (599/1008) of participants

Table 2: Proportion achieving SVR by patient characteristics at baseline

	SVR % (95% CI)
Biologic sex	
Male	93.4 (91.6-95.3)
Female	98.1 (96.7-99.6)
Age	
< 30 years	100.00 (88.4-100.0) [2]
30-39 years	96.2 (89.2-99.2)
40-49 years	94.2 (89.3-97.3)
50-59 years	96.3 (93.9-98.0)
60 + years	94.1 (91.0-96.4)
HIV	
Negative	94.9 (93.4-96.4)
Positive	91.1 (82.8-99.4)
Injection drug use[1]	
Past/Current	94.4 (91.8-97.0)
Never	96.6 (94.6-98.7)
Genotype	
1a	95.3 (93.1-97.0)
1b	95.5 (91.4-98.1)
1, no sub-type	96.2 (89.3-99.2)
2	91.3 (82.0-96.7)
3	92.9 (87.3-96.5)
4	100.00 (78.2-100.0)[2]
6	100.00 (29.2-100.00) [2]
Metavir Score, % (n)	
F0-F1	96.6 (93.7-98.4)
F2-F3	95.3 (92.0-97.5)
F4	92.6 (89.0-95.3)

[1] Data on injection drug use status was only available for 59.4% (599/1008) of participants
[2] 1-sided, 97.5% confidence interval due to low numbers

Figure 2. SVR rates by genotype

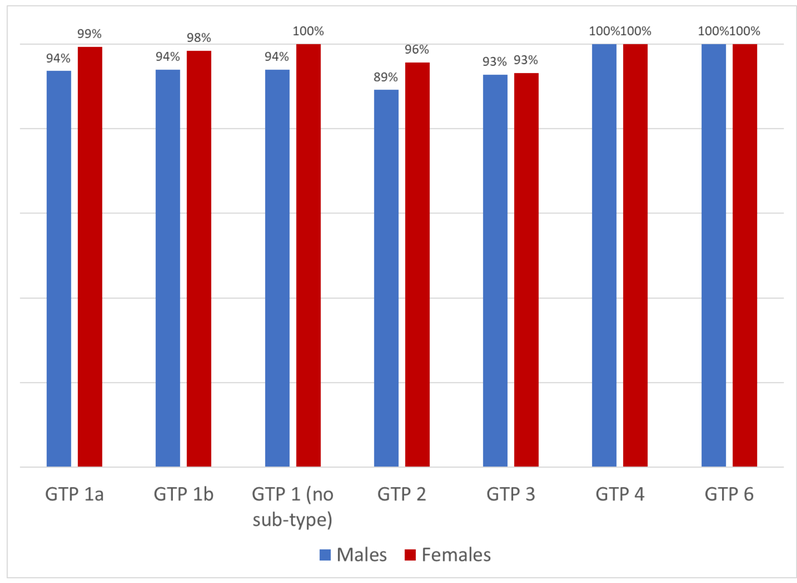

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Figure 3. SVR rates in males by age group

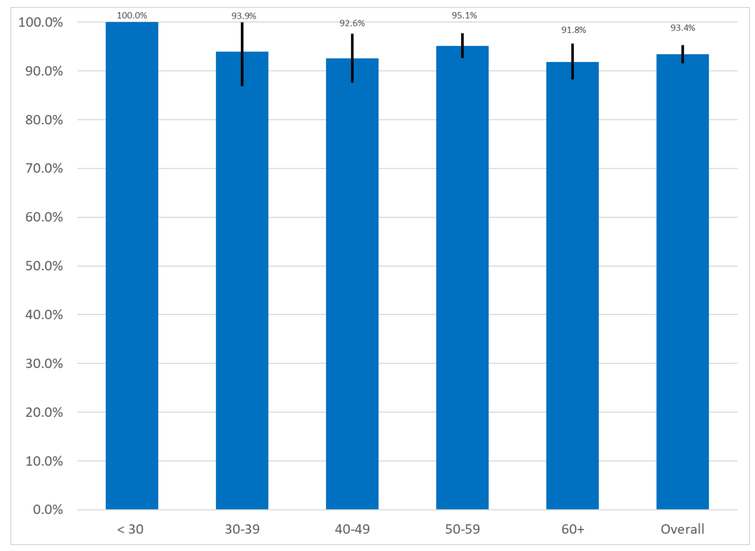
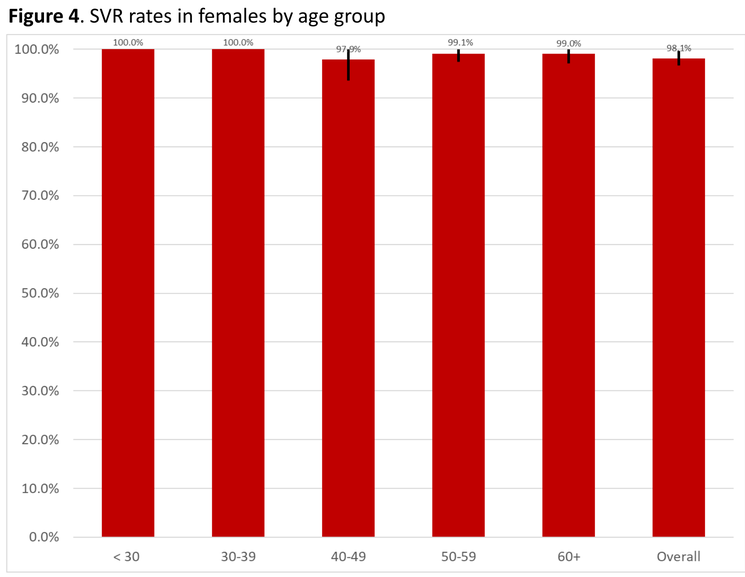


Figure 4. SVR rates in females by age group



Discussion

- Evidence has suggested that DAAs are efficacious regardless of patient characteristics; however, there appear to be an increasing number of studies published since DAAs became available that also support higher SVR rates in females[1-2,4-6] .
- Similar findings supporting improved SVR in females were also previously found in studies conducted using interferon-containing regimens.[7,8]
- Pharmacokinetic and pharmacodynamic differences in response to various drug treatments are common and related to a number of key differences between the sexes.[9]
- It has been established that the disease course of HCV in women is different from their male counterparts. Women are more likely to spontaneously clear the virus, and less likely to progress to cirrhosis. Studies have posited this is due to estrogen's antifibrogenic action which inhibits stellate cells.[10]

Conclusion

- Evidence suggests that females are more likely to achieve SVR than males.
- The exact effect which results in the differences in SVR observed in this study and elsewhere remains unclear at this time. The CANUCH prospective national registry may help further knowledge on if this trend continues.

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