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Sex Differences in Extrahepatic Outcomes After Antiviral Treatment for Hepatitis C

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INTRODUCTION: Despite recognized differences in the rates of cardiovascular and renal disease between men and women in the general population, studies of the downstream effects of antiviral treatment for hepatitis C (HCV) have not investigated differences in outcomes based on sex. We analyzed sex differences in risk of acute coronary syndrome (ACS), end-stage renal disease (ESRD), and ischemic stroke by treatment and response in a large US-based multisite cohort of HCV patients.

METHODS: Observation started at the HCV diagnosis date (untreated) or last antiviral treatment start (treated). Treatment selection bias was addressed using an inverse probability-weighting approach. We estimated the effect of treatment on the cumulative incidence of outcomes using the Fine-Gray method (subdistribution hazard ratios [sHR] and 95% confidence intervals [95% CI]). Death was a competing risk.

RESULTS: Roughly 40% of 15,295 HCV patients were women. After controlling for other risk factors, sustained virological response (SVR) (interferon-based [IFN] or direct-acting antiviral [DAA]) significantly reduced risk of all outcomes, particularly among female patients. Female patients who achieved SVR after IFN-based treatment had significantly lower risk of ACS compared with male patients with SVR from either treatment type (sHR 0.45 [95% CI 0.35–0.59] vs 0.81 [95% CI 0.69–0.96, for DAA SVR] and sHR 0.72 [95% CI 0.62, 0.85, for IFN SVR]). Successful treatment seemed to be most protective against ESRD; female patients who achieved SVR were at 66%–68% lower risk than untreated patients (sHR 0.32 [95% CI 0.17–0.60 for DAA SVR] and 0.34 [95% CI 0.20–0.58 for IFN SVR]), whereas men were at 38%–42% lower risk (sHR 0.62 [95% CI 0.46–0.85 for DAA SVR] and 0.58 [95% CI 0.43–0.76 for IFN SVR]). IFN treatment failure significantly increased risk of all outcomes by 50%–100% among female patients. Compared with no treatment, female patients who experienced IFN treatment failure were at 63% increased risk of ACS (sHR 1.63 [95% CI 1.35–1.96]), almost twice the risk of ESRD (sHR 1.95 [95% CI 1.43–2.66]) and 51% increased risk of stroke (sHR 1.49 [95% CI 1.11–2.00]).

DISCUSSION: SVR reduced the risk of extrahepatic complications, particularly in females. The significantly increased risk associated with IFN TF in women—a subset who represented roughly 10% of that group—underscores the importance of prioritizing these patients for DAA treatment irrespective of the fibrosis stage.

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/AJG/B810>.

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INTRODUCTION

Chronic infection with hepatitis C (HCV) is associated with increased risk of a number of extrahepatic manifestations, including type 2 diabetes (T2D) and cardiovascular conditions (1). The Chronic Hepatitis Cohort Study (CHeCS) recently showed that HCV patients who achieved sustained virological

response (SVR) to antiviral treatment were less likely to develop T2D (2) and that patients with existing T2D were less likely to experience acute coronary syndrome (ACS), ischemic stroke, and end-stage renal disease (ESRD) (3). To date, only a handful of studies have investigated the impact of SVR on long-term extrahepatic manifestations among HCV patients without T2D; in

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general, it seems that SVR reduces risk of cardiovascular events, stroke, and renal disease. These studies have some limitations, however, in the comparisons between patients by treatment status (treated or untreated), outcome (SVR or treatment failure [TF]), or type (interferon-based [IFN] or direct-acting antiviral [DAA] therapies) (4–6).

To date, only one large study ($N > 160,000$) has compared the risk of long-term outcomes across both IFN-based and DAA treatment, but this study did not distinguish between SVR from DAA and IFN-based regimens, and the cohort was overwhelmingly ($>96\%$) male (7). There are known sex differences in the presentation of HCV, including disease progression, prevalence of extrahepatic manifestations, and response to treatment (8–10). Similarly, there are well-recognized differences in risk profiles for cardiovascular and renal disease between men and women (11–13). As a result, it is imperative that women are proportionately represented in studies of the relationship between HCV treatment status and cardiovascular outcomes to allow for conclusions that are generalizable to the wider population. The CHeCS includes a geographically and racially diverse sample of more than 15,000 HCV patients (40% female) drawn from 4 large health systems in the United States. Using the comprehensive electronic health record data, we investigated the impact of treatment status (untreated, treated with IFN, and treated with DAA) and outcome (SVR or TF) on risk of incident ACS, ESRD, and ischemic stroke.

METHODS

Patient population

CHeCS is a retrospective/prospective, observational study that includes patients from 4 large US health systems—Geisinger Clinic (Danville, PA), Henry Ford Health System (Detroit, MI), Kaiser Permanente Hawai'i (Honolulu, HI), and Kaiser Permanente Northwest (Portland, OR). CHeCS follows all guidelines of the US Department of Health and Human Services regarding protection of human subjects; study protocols were approved by the institutional review board at each participating site. The CHeCS study design has been described previously (14). Briefly, electronic administrative data and electronic health records for patients older than or equal to 18 years who received health services at any study site from January 1, 2006, to December 31, 2016, were used to identify study candidates; eligibility was confirmed with medical chart abstraction.

For this analysis, the start of the observation period (“index date”) was defined as the date of last treatment initiation for treated patients. For untreated patients, the index date was the dates of HCV diagnosis. Patients were excluded if they had hepatitis B virus coinfection.

HCV treatment status and response

Detailed antiviral medication data (drug name and start/stop dates) were collected via chart abstraction. Data on routine HCV RNA quantification tests were obtained via the electronic health record. Patients with ongoing HCV therapy without sufficient follow-up to assess SVR (defined as undetectable viral RNA loads ≥ 12 weeks post-therapy initiation) were excluded from the analyses. Patients were classified into one of 5 treatment status/outcomes groups—(i) DAA SVR, (ii) DAA TF, (iii) IFN SVR, (iv) IFN TF, and (v) untreated.

Outcomes of interest

All eligible patients were followed for 3 extrahepatic outcomes: (i) ACS, (ii) ESRD (15,16), and (iii) ischemic stroke. Outcomes were defined using the primary International Classification of Diseases (ICD)9-CM/ICD10-CM codes (detailed in Supplementary Table 1, Supplementary Digital Content 1, <http://links.lww.com/AJG/B810>). Follow-up continued through the earliest date of an outcome of interest, patient death, or last administration date. The maximum follow-up was truncated at 5 years. Patients with a history of any of the outcomes of interest before index were excluded from the analyses for that outcomes.

Potential confounding factors

Index date demographic information included patient age, sex, race/ethnicity, type of insurance, and study site. Clinical variables included body mass index, T2D, hemoglobin A1c laboratory results, antiviral treatment history, HCV genotype, glomerular filtration rate category, Charlson-Deyo comorbidity indices (calculated from inpatient, outpatient, and claims data for 12 months before the index date) (17), hyperlipidemia, hypertension, ever use of statins, Fibrosis-4 Index (FIB-4—a biomarker index for liver fibrosis and cirrhosis), and cirrhosis at any time before index date. Diabetes, hyperlipidemia, and hypertension within 1 year pre-/post-index date were ascertained using ICD9/10 codes (see Supplementary Table 1, Supplementary Digital Content 1, <http://links.lww.com/AJG/B810>). Pharmacy order and fill data were used to define statin use. Owing to the observational nature of the study, availability of cirrhosis data varied. Roughly 20% of our sample had liver biopsy/vibration controlled transient elastography data and 60%–70% had laboratory data for calculation of FIB-4. To overcome this variation, we implemented a hierarchical classification algorithm to identify cirrhosis—(i) decompensated cirrhosis identified using our validated Classification and Regression Tree model (18), (ii) “F4” liver biopsy or transient elastography results >12.5 kPa (19), (iii) FIB-4 >5.88 (20), and (iv) presence of ICD9/10 diagnosis codes for cirrhosis in the electronic health record.

Statistical analysis

To account for confounding due to treatment selection bias, we used a propensity score approach based on a generalized boosted model (21), with treatment as the outcome variable and index-date demographic variables and clinical risk factors as covariates. Propensity scores were calculated for patients in 3 groups—DAA treated, IFN treated, and never treated—using a generalized boosted model. Because of the missing data, multiple imputation by chain equations (22) was implemented under a missing at random assumption. The propensity score was then averaged across multiple imputations. Balance of index-date covariates between treated and untreated patients was assessed before and after inverse propensity weighting (IPW) (23,24). A standardized difference with an absolute value < 0.2 indicates balance between the groups (25). The treatment effect on risk of each outcome of interest was tested using Fine-Gray subdistribution hazards models (26), adjusted for IPW. Death was considered as a competing risk.

Given recognized differences in risk of cardiovascular disease, we also tested for interactions between treatment status/response and sex. Significant treatment-by-sex interactions ($P < 0.05$) were further evaluated to determine whether they were quantitative (different in magnitude of effect) or qualitative (different in direction of effect).

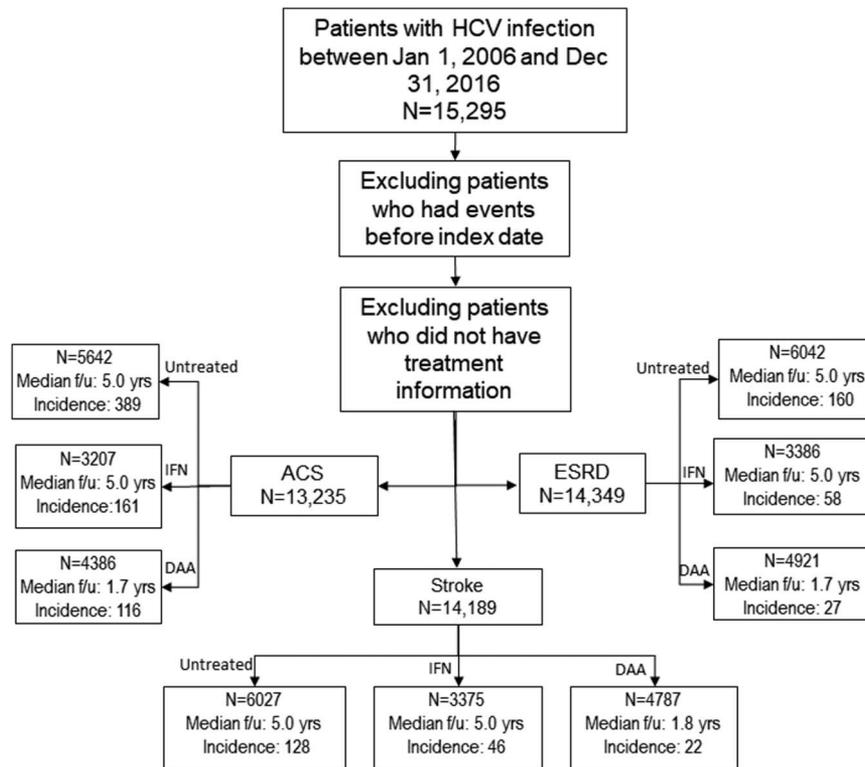


Figure 1. Flow chart of HCV patient samples for each outcome of interest (ACS, ESRD, and ischemic stroke) by treatment status (untreated, treated with IFN, and treated with DAA). ACS, acute coronary syndrome; ESRD, end-stage renal disease; DAA, direct-acting antivirals; IFN, interferon-based regimens.

We also conducted several sensitivity analyses. In the first sensitivity analysis, to ensure an appropriate understanding of the relationship between HCV treatment and the outcomes of interest, we calculated cause-specific hazards for each outcome because the effect of a covariate on the cause-specific hazard for a particular cause may differ from its effect on the cumulative incidence when competing risks are present (27). Second, to address possible violations of the proportional hazards assumption with the above models, we used an alternative approach—the restricted mean survival time (RMST) method—which represents the area under the survival curve from time 0 to a specific follow-up time point; this can be interpreted as the average time until an event occurs during a defined time period. Use of RMST in the setting of competing risks and IPW has been described by Calkins et al. (28); death was considered a competing risk. Confidence intervals were obtained by 10,000 bootstraps; corresponding *P*-values were calculated by 10,000 permutations. Finally, for our last sensitivity analysis, we omitted both the Charlson-Deyo comorbidity score and the indicator for cirrhosis to determine whether the treatment effect observed in the main analysis remained consistent despite the omission of important confounders; a robust treatment effect indicates that unobserved confounding can be disregarded (29).

RESULTS

Figure 1 outlines the number of patients included in the analysis for each of the outcomes of interest and median follow-up time and number of events, stratified by treatment status. Overall, among 15,295 CHeCS HCV patients, 6,972 (43.6%) were untreated, 4,843 received DAA (SVR = 91.4%), and 3,467 received IFN-based treatment (SVR = 54.2%). Average patient age at

index was 52 years. Patient characteristics and comorbidities that are commonly associated with the outcomes of interest were balanced and within the desired range of standardized difference after propensity score weighting. After excluding patients who had experienced an outcome of interest before the index date, there were 13,235 patients for the analysis of ACS, 14,349 for ESRD, and 14,189 for ischemic stroke. For the analysis of ACS, 4,386 patients in the sample were treated with DAA, 4,150 of whom (94.6%) achieved SVR, 3,207 received IFN-based therapy, and 1814 of whom (56.6%) achieved SVR. Similar percentages were observed in the analyses of ESRD and ischemic stroke (Figure 1). Median follow-up for DAA treated patients was 1.8 years. Table 1 displays details of the analytical samples used for each outcome of interest by treatment status and sex. Female patients represented roughly 40% of each analytical sample. Hazard ratio estimates with fewer than 5 events were deemed unreliable; as a result, the DAA TF group (*n* = 236) was excluded in the subsequent analyses. Treatment-by-sex interactions were significant for all 3 outcomes (ACS, ESRD, and ischemic stroke; *P* < 0.0001); thus, the results for each outcome are presented stratified by sex.

Figure 2 displays the adjusted subdistribution hazard ratios (sHR) for each outcome of interest by treatment status, stratified by sex. In general, SVR from either DAA or IFN-based treatment was associated with reduced risk of outcomes compared with no treatment. Ischemic stroke was the exception; risk among female patients with IFN SVR and male patients with DAA SVR trended lower but was not significantly different than that among untreated patients. Female patients who achieved SVR after IFN-based treatment had significantly lower risk of ACS compared with male patients with SVR from either treatment type (sHR 0.45

Table 1. Analytic sample, events of interest, and crude incidence rates per 1,000 person-years for ACS, ESRD, and ischemic stroke for each treatment type/status group

Treatment type/status	Female (n)	%	Male (n)	%	Total	No event	Death	Event of interest	Incidence rate
Analytical sample									
ACS									
DAA SVR	1,657	40	2,493	60	4,150	3,944	93	113	13.7
DAA TF	85	36	151	64	236	200	33	3	7.6
IFN SVR	774	43	1,040	57	1,814	1,688	43	83	9.9
IFN TF	518	37	875	63	1,393	1,190	125	78	12.5
Untreated	2,377	42	3,265	58	5,642	4,604	649	389	16.9
Total	5,411	41	7,824	59	13,235				
ESRD									
DAA SVR	1,829	39	2,816	61	4,645	4,499	120	26	2.8
DAA TF	95	34	181	66	276	234	41	1	2.2
IFN SVR	808	42	1,114	58	1,922	1,861	46	15	1.7
IFN TF	542	37	922	63	1,464	1,286	135	43	6.5
Untreated	2,505	41	3,537	59	6,042	5,114	768	160	6.4
Total	5,779	40	8,570	60	14,349				
Ischemic stroke									
DAA SVR	1,790	40	2,728	60	4,518	4,379	118	21	2.3
DAA TF	92	34	177	66	269	228	40	1	2.3
IFN SVR	803	42	1,107	58	1,910	1,834	49	27	3.0
IFN TF	541	37	924	63	1,465	1,296	150	19	2.8
Untreated	2,493	41	3,534	59	6,027	5,086	813	128	5.1
Total	5,719	40	8,470	60	14,189				

ACS, acute coronary syndrome; DAA, direct-acting antivirals; ESRD, end-stage renal disease; IFN, interferon-based regimens; sHR, subdistribution hazard ratios; SVR, sustained virological response; TF, treatment failure.

[95% confidence interval {CI} 0.35–0.59] for women vs 0.81 [95% CI 0.69–0.96, for DAA SVR] and 0.72 [95% CI 0.62–0.85, for IFN SVR] for men. Successful treatment also protected against ESRD; female patients who achieved SVR were at 66%–68% lower risk than untreated patients (sHR 0.32, 95% CI 0.17–0.60 for DAA SVR; 0.34, 95% CI 0.20–0.58 for IFN SVR), whereas male patients were at 38%–42% lower risk (sHR 0.62, 95% CI 0.46–0.85 for DAA SVR; 0.58, 95% CI 0.43–0.76 for IFN SVR).

There was a significant qualitative sex-by-treatment status interaction for patients who experienced IFN TF. Although IFN TF was associated with reduced risk of ACS and stroke for male patients, it was associated with significantly increased risk of all outcomes for female patients. Compared with no treatment, female patients who experienced IFN TF were at 63% increased risk of ACS (sHR 1.63 [95% CI 1.35–1.96]), almost twice the risk of ESRD (sHR 1.95 [95% CI 1.43–2.66]), and 51% increased risk of stroke (sHR 1.49, [95% CI 1.11–2.00]). By contrast, male patients who experience at IFN TF had significantly lower risk of ACS and stroke and increased but not significantly higher risk of ESRD compared with untreated patients.

Figure 3 displays comparisons for female vs male patients for risk of ACS, ESRD, and ischemic stroke within each treatment status group. Risks for ACS and ESRD were lower for female than that for male patients in each treatment category except for

IFN TF; in that category, risk of ACS was 79% higher (sHR 1.79 [95% CI 1.46–2.19]) and risk of ESRD was similar (sHR 0.91 [95% CI 0.69–1.20]) in female patients compared with male patients. By contrast, risk of stroke varied by treatment type. Female patients who were untreated or achieved SVR after IFN-based treatment had similar risk of stroke to male patients, but those with DAA SVR had roughly half the risk (sHR 0.42 [95% CI 0.23–0.76]) and those with IFN TF had almost 3 times the risk (sHR 2.99 [95% CI 2.04–4.39]) of male patients in the same treatment groups.

Supplementary Figure 1, Supplementary Digital Content 1, <http://links.lww.com/AJG/B810> displays the results of the cause-specific hazard model (a sensitivity analysis). Results from the cause-specific model were consistent in magnitude and significance with those of the main analysis, allowing us to conclude that competing risks did not influence our observations. Supplementary Figures 2 and 3, Supplementary Digital Content 1, <http://links.lww.com/AJG/B810> detail our second sensitivity analysis. When comparing RMST at each year, IFN SVR patients averaged longer time to ACS at 5 years compared with those who were untreated (RMST ratio = 1.02; $P = 0.022$); DAA SVR patients also had longer times to ACS, but these differences were not statistically significant. In sex-stratified results, female DAA SVR patients exhibited the longest ACS-

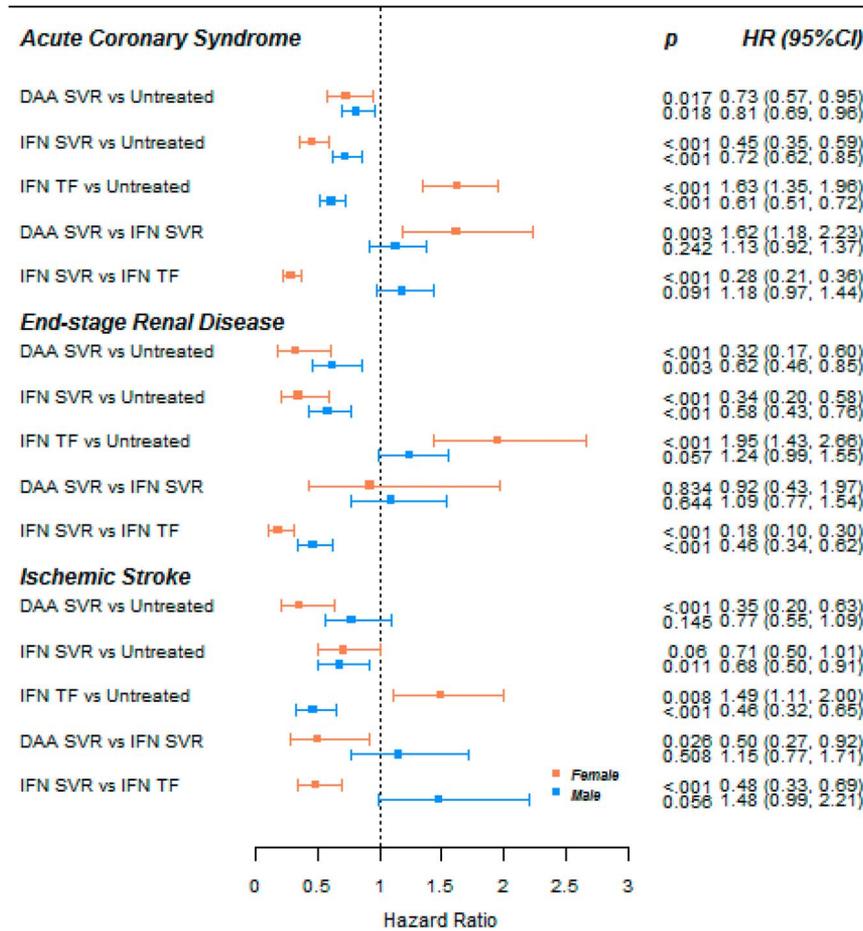


Figure 2. Fine-Gray sHR for each outcome of interest by treatment type (untreated, treated with IFN, and treated with DAA) and status (SVR or TF), stratified by sex (orange, female; blue, male). DAA, direct-acting antivirals; IFN, interferon-based regimens; sHR, subdistribution hazard ratios; SVR, sustained virological response; TF, treatment failure.

free time compared with other groups, starting at year 2, but this was only statistically significant compared with the IFN TF group. For ESRD, SVR (regardless of treatment type) was associated with statistically significantly longer time to ESRD compared with untreated patients at each year post-treatment. IFN SVR patients also demonstrated longer ESRD-free time at years 3, 4, and 5 post-treatment, compared with IFN TF patients. We observed similar patterns in sex-stratified analyses. For ischemic stroke, treated patients showed longer time to stroke compared with untreated patients. In the combined analysis, this only reached significance for DAA SVR patients and IFN TF patients. In the sex-stratified analysis, these differences were more common among female patients. In contrast to the main analysis, we did not observe higher risk for the outcomes of interest among IFN TF patients. This is likely due to proportional hazards assumptions in the Fine-Gray model. In summary, the RMST results were generally consistent with the traditional hazard ratio approach; the failure of some RMST ratios to achieve statistical significance is likely because of different model assumptions and power.

DISCUSSION

In a large, racially diverse cohort of HCV patients, we found that patients who achieved SVR either with DAA or IFN-based

treatments were at significantly reduced risk—20%–50% lower overall—of ACS, ESRD, and stroke compared with untreated patients. This finding contributes to the larger body of research emphasizing the long-term extrahepatic benefits of successful antiviral treatment, even after accounting for possible bias in selection for HCV treatments and for traditional risk factors (e.g., T2D, hypertension, hyperlipidemia, and e-glomerular filtration rate) for cardiovascular and renal disease. Characteristics of different treatment groups were balanced after IPW. (see Supplementary Tables, Supplementary Digital Content 1, <http://links.lww.com/AJG/B810>).

We observed a number of quantitative and qualitative interactions between treatment status and sex. Female patients generally seemed to benefit more from SVR than male patients, although these differences did not always reach statistical significance. Given the documented sex differences in both HCV progression and complications (8–10), as well as overall lower risk of cardiovascular and renal disease among female patients (11–13), this observation is perhaps not surprising. We note that risks also varied by specific treatment regimen among female patients who achieved SVR—compared with IFN SVR, DAA SVR was less protective against ACS and more protective against stroke. Notably, failure of IFN-based treatment (IFN TF) was associated with 50%–100% increased risk of all outcomes

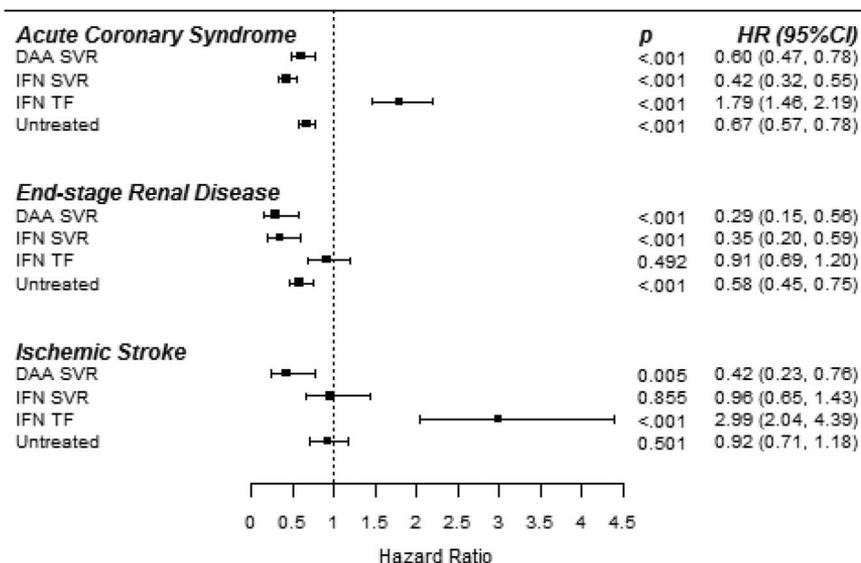


Figure 3. Fine-Gray sHR comparing female patients vs male patients for each outcome of interest within each treatment type (untreated, treated with DAA, treated with IFN) and status (SVR or TF). DAA, direct-acting antivirals; IFN, interferon-based regimens; sHR, subdistribution hazard ratios; SVR, sustained virological response; TF, treatment failure.

compared with no treatment, but only among female patients; IFN TF among male patients, however, was associated with unchanged or decreased risk of all outcomes of interest. Despite the replacement of IFN-based treatments by DAA regimens as standard of care, almost 10% of the women in our “real-world” cohort fell into the category of IFN TF (living and not having received DAA therapy) at the time of this analysis. Our results highlight the importance of identifying these patients with previous IFN TF and prioritizing them for DAA treatment.

We believe that this is the first analysis of the effect of HCV treatment on extrahepatic outcomes across 2 treatment eras (IFN and DAA) and by treatment response (SVR or TF), as well as untreated patients. Our findings are generally consistent with a similar study of IFN-treated patients from Taiwan (4) who found that treatment reduced risk of ACS and stroke by 23% and 38%, respectively, vs 37% and 31% among our IFN SVR sample. However, that study observed far greater reduction in risk for ESRD (85% vs the 49% reduction observed in our cohort compared with untreated patients). This may be because the comparison groups in this analysis (ever IFN treated vs untreated) differed from our present analysis (IFN SVR vs untreated and vs IFN TF); it is also possibly the high rates of chronic kidney disease—including glomerulonephritis, a common extrahepatic manifestation of HCV—in Taiwan may contribute to these observed differences (30). Similarly, our findings are also generally consistent with those of a recent study of patients who achieved SVR after IFN-based treatment (6); this study also found that female patients benefited more from SVR regarding risk for ACS and ESRD, although differences in how outcomes were defined and differences in how non-SVR patients were grouped make direct comparisons not possible. Hazard ratios for specific cardiovascular outcomes were not reported by treatment type and response for the recent large US Veterans’ Administration study (7), but incidence rates for each outcome were similar in SVR and non-SVR patients. By contrast, we observed significantly higher risk of these outcomes among female patients with TF. This difference may be an artifact of the primarily male makeup (96%) of the veteran-based cohort.

Our study has some limitations. Although it was designed to evaluate differences in the rate of long-term extrahepatic outcomes associated with chronic HCV by sex and treatment type, it was not designed to illuminate specific reasons that may underlie those differences. Previous research has shown that progression of liver fibrosis and cirrhosis, as well as rates of SVR, vary by sex among patients with HCV; studies of pre- and post-menopausal women suggest that hormonal factors may play a part in these differences (8–10). We believe it is reasonable to suggest that, coupled with overall lower risk of cardiovascular and renal disease among women than men (11–13), such differences likely underlie the lower rates of poor outcomes observed among female patients who achieved SVR, compared with male patients. By contrast, there are no long-term studies that can adequately explain why we observed higher rates of poor outcomes only among female patients who experienced IFN TF. However, a few studies from the era of IFN regimens reported the sex of participants when describing cardiovascular side effects during antiviral treatment for HCV. For example, in one study, a slightly larger proportion of female patients experienced complications such as cardiac ischemia during treatment compared with male patients, although these differences were nonsignificant in this relatively small sample, which was also not stratified by treatment outcome (31); a similar report described that adverse cardiac outcomes from IFN therapy were confined to female patients in a small sample (32). This suggests that perhaps there are sex differences in how IFN-based treatment affects the cardiovascular system. Notably, in our sample, treatment duration did not vary between IFN SVR and TF patients—suggesting that neither early discontinuation nor longer duration of treatment are related to development of the outcomes of interest.

As expected in a real-world study, a portion of our patients remained untreated with DAA after IFN TF. We recently conducted a survey of a subset of HCV patients in our cohort who were eligible for DAA treatment. Among roughly 200 patients who did not initiate DAA therapy, more than one-third were never referred to a specialist, 12% did not know why they had not been referred, 11% had more pressing medical issues, 8% reported not feeling ill, 10% were unable to pay for additional care or lacked

transportation, and 16% reported “other reasons.” (33) At one study site, a pilot outreach program to increase treatment rates among DAA eligible patients had a low response rate, with patients citing similar reasons to those described above, especially that they “did not feel sick” or had more pressing medical issues (data not published).

There are also limitations inherent in the use of observational data drawn from “real-world” patients. To address missing baseline data, we used multiple imputation. To control for treatment bias, propensity score weighting was used; this accounted for differences in fibrosis/cirrhosis status as well as Charlson-Deyo comorbidity scores—which include a number of cardiovascular and renal conditions, such as history of transient ischemic attacks. We also performed multiple sensitivity analyses (a cause-specific hazards analysis and RMST analysis) to ensure that appropriate conclusions were drawn. The results of all sensitivity analyses were consistent with the main analysis and support our conclusions. A considerable strength of our study is our analysis of both treatment status and response—untreated, IFN SVR, IFN TF, and DAA SVR—stratified by patient sex. This granularity allowed us to show a novel effect of IFN TF that was confined only to female patients. A future analysis will investigate risk factors that may be associated with poor outcomes in this group.

In summary, we observed that achieving SVR after either IFN-based or DAA regimens reduced risk of ACS, ESRD, and stroke; female patients largely seemed to benefit more than male patients within each treatment group. Male patients did not demonstrate any difference in benefit between IFN and DAA SVR, whereas female patients derived more benefit from IFN SVR regarding ACS and from DAA SVR regarding stroke. Importantly, female patients who experienced IFN TF were at increased risk of all outcomes, irrespective of severity of fibrosis or cirrhosis, underscoring the importance of identifying women who have previously failed IFN-based treatment and prioritizing them for DAA therapy.

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CONFLICTS OF INTEREST

Guarantor of article: Jia Li, PhD.

Author contributions: Responsibility for the integrity of the work as a whole, from inception to the published article: J.L. Study concept and design: J.L., S.C.G., and M.L. Acquisition of data: S.C.G., M.L., J.A.B., M.A.S., and Y.G.D. Analysis and interpretation of data: J.L., Y.Z., S.T., S.C.G., L.B.R., and M.L. Drafting of the manuscript: J.L., S.C.G., L.B.R., S.T., and M.L. Critical revision of the manuscript for important intellectual content: J.L., S.C.G., T.Z., L.B.R., S.T., J.A.B.,

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Study Highlights

WHAT IS KNOWN

- ✓ Successful antiviral treatment for HCV may result in reduced risk for long-term extrahepatic outcomes, but this has not been examined sufficiently among female patients.

WHAT IS NEW HERE

- ✓ We found that women particularly benefited from successful treatment regarding reduced risk for ACS, ESRD, and ischemic stroke compared with patients who did not receive treatment or those who experienced TF. For stroke, risk was lower only among female patients who achieved SVR with DAA therapy. On the other hand, women who experienced failure of IFN treatment were at higher risk of all outcomes compared with untreated patients.

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