Observational Study

Direct acting antiviral HCV treatment does not influence renal function

Matt Driedger, MD, Chrissi Galanakis, MSc, Curtis Cooper, MD, FRCPC

Abstract

HCV infection is associated with chronic kidney disease due to several mechanisms. Patients treated with interferon-based regimens demonstrate improved renal function and reduced incidence of chronic kidney disease. There is scarce evidence on the effect of direct acting antiviral regimens (DAAs) on renal function.

We evaluated serial measures of renal function in a cohort of HCV-infected participants following completion of DAA-based treatment regimens.

Measures of glomerular filtration rate (GFR) were estimated by the CKD-EPI equation. Data was recorded at end of treatment, and at 6–12 months, 12–24 months, and greater than 24 months following treatment completion. Group-based trajectory modeling was used to determine distinct GFR trajectories. Predictors of group membership were determined by multinomial regression analysis.

Six trajectories were identified. One trajectory comprising 27% of the cohort demonstrated declining renal function and the others demonstrated no change in renal function over time. Baseline GFR did not predict SVR. Diabetes was associated with lower post-treatment GFR but patients with diabetes did not demonstrate a decrease in GFR over the period of evaluation. Cirrhosis and SVR were not significant predictors of GFR or GFR trajectory.

There is no clinically relevant change in renal function among the majority of HCV-infected patients following completion of DAA-based treatments. Renal function does not influence the efficacy of DAA-based regimens. No consistent effect of DAA treatment and/or SVR on renal function was observed over a 2-year period following treatment completion.

Abbreviations: DAA = direct acting antiviral, GFR = glomerular filtration rate, HCV = hepatitis C virus, IFN = interferon, RBV = ribavirin, SOF = sofosbuvir, SVR = sustained virological response.

Keywords: direct acting antivirals, HCV treatment, hepatitis C, renal function

1. Introduction

HCV infection leads to a number of extra-hepatic manifestations resulting in morbidity and mortality, including renal dysfunction.[1,2] There is a well-established association between HCV infection and increased incidence of chronic kidney disease.[3-5] HCV infection is also associated with increased incidence of end-stage renal disease[6,7] as well as mortality among patients with existing end-stage renal disease.[8] Renal impairment in HCV infection is associated with chronic kidney disease due to several mechanisms. Patients treated with interferon-based regimens demonstrate improved renal function and reduced incidence of chronic kidney disease. There is scarce evidence on the effect of direct acting antiviral regimens (DAAs) on renal function.

In the direct acting antiviral (DAA) era, severe renal impairment (eGFR < 30 ml/min/1.73 m²) does not appear to negatively influence SVR rates, and has not been associated with greater adverse event incidence in HCV-infected patients receiving DAA treatment.[8-11] Sofosbuvir (SOF) is the only commonly used DAA that is primarily cleared renally. Despite initial concerns, recent literature suggests that it is safe and effective in patients with severe renal impairment.[12,16-20]

The effect of sustained virological response (SVR) on renal function is well-established in the context of interferon (IFN) based regimens. Patients who achieved SVR with IFN regimens have a reduced incidence of chronic kidney disease and end-stage renal disease.[21-23] A meta-analysis of eleven trials demonstrated that SVR with IFN-based regimens results in decreased proteinuria and creatinine levels in patients with HCV-associated glomerulonephritis.[24] One study demonstrated remission of nephropathy in 75% of patients who had pre-existing mixed cryoglobulinemia.[25]

There is relatively scarce evidence suggesting DAA treatment may improve renal function. This includes 2 trials of 19 renal transplant patients and 7 patients with cryoglobulinemia-associated chronic kidney disease, respectively.[27] and 2 case studies of patients with mixed cryoglobulinemia.[28,29] There have also been contradicting reports of new-onset glomerular disease during[30] or following[31] completion of DAA regimens in patients without pre-existing renal disease.
In this current HCV cohort analysis, we sought to determine if renal function is influenced following completion of therapy with interferon-free DAA regimens. We also investigated whether renal function influences treatment efficacy.

2. Patients and methods

All HCV-infected patients receiving DAA-based treatment at The Ottawa Hospital Viral Hepatitis Program clinic from July 2012 to October 2016 were included in this analysis (The Ottawa Health Science Network Research Ethics Board 2004–196). Patients who discontinued treatment or were lost to follow-up with missing sustained virological response (SVR) outcome data were excluded.

Demographic and clinical data including age, sex, race, HCV viral load, and genotype as well as HIV and hepatitis B status were recorded. Transient Elastography (Fibroscan) was used to quantify fibrosis by liver stiffness measures. Inflammation and steatosis were measured by Controlled Attenuation Parameter (CAP) scores. Cirrhosis was defined as a liver stiffness score of ≥12.5 kPa. Diabetes was defined by random glucose readings >11.0 mmol/L, HbA1c > 6.5% or if documented in the medical chart. GFR was calculated by the CKD-EPI equation. Chronic kidney disease was defined as GFR <60 ml/min/1.73 m². GFR was recorded at treatment baseline (pre-DAA treatment) and at 6-month post-treatment intervals. The mean post-treatment GFR was calculated for the following time points: 0–6 months (0 months indicating treatment completion), 6–12 months, 12–24 months, and greater than 24 months. In the post-treatment GFR analysis, only the most recent treatment round was included for cases with multiple treatments. Multiple treatment rounds were included in the analysis if the time between treatments (from end of treatment to the new treatment start) was greater than 12 months. GFR data was censored prior to treatment start for cases that re-initiated treatment.

Characteristics of patients achieving SVR were compared to those who failed DAA treatment using Chi-Squared, Fisher exact test, t tests or Mann–Whitney U tests. Predictors of SVR were assessed by logistic regression. Group-based trajectory modeling was used to determine changes in GFR post-DAA treatment. Various models were evaluated using the proc traj SAS macro to determine the number of distinct GFR trajectories and their respective slopes. Dropout probability was also included in the model to account for attrition. The model with the best Bayes Information Criterion was selected. Group membership to a given trajectory was determined by the analysis, whereby each subject had a calculated posterior probability of membership for each of the groups in the model. The subject was assigned to the group with the highest posterior probability. Factors determining group membership were assessed by multinomial logistic regression analysis. Analyses were performed with SPSS version 25.0 (IBM Corp, 2017) and SAS 9.4 (SAS Institute, Cary NC).

3. Results

Patient characteristics are presented in Table 1. The SVR analysis included 425 treatments. The mean age of participants was 56 years (SD 9.4). Eighty one percent of participants were Caucasian, and 64% were male. Genotype 1 was most common (n = 313, 73%), followed by genotype 3 (13%), and genotype 2 (8%). The mean baseline GFR was 90 ml/min/1.73 m², and 8% of participants had chronic kidney disease at baseline. The mean transient elastography score was 18.1 kPa, and 61% of participants had advanced fibrosis (>9.0 kPa). The mean ALT was 99 IU/L (SD 76.1) and mean AST was 77 IU/L (SD 52.4). Mean HCV viral load was 3.3 × 10⁶ copies/ml (SD 5.0 × 10⁶). Fourteen different treatment regimens were included. The majority of treatments included sofosbuvir (SOF) (n = 377, 87%). Forty percent of treatments included ribavirin (RBV), the largest proportion of which comprised of 24-week duration SOF-RBV regimens for genotypes 2 and 3 (39% of all RBV-containing regimens). SOF-containing regimens included SOF with RBV (14% of all treatments), ledipasvir+/-RBV (55%), simprevir+/-RBV (12%), daclatasvir+/-RBV (3%), and velpatasvir (3%). Non-SOF containing regimens included obatitasvir/paritaprevir/ritonavir with dasabuvir +/- RBV (10%) and elbasvir/grazoprevir +/- RBV (3%). The majority of treatments were 8–12 weeks (79%), and 21% were 16–24 weeks in duration. Fifteen percent of patients had diabetes at baseline and 6% were HIV co-infected.

Predictors of SVR were determined through logistic regression (Table 2). Baseline GFR category did not predict SVR in univariate or multivariate analyses. Recipients of treatment regimens that included RBV were less likely to achieve SVR in univariate (OR 0.33, 95% CI 0.09–0.43) and multivariate (OR 0.38, 95% CI 0.15–0.97) analyses. Genotype 3 and “other” genotype (genotype 4 and mixed genotypes) were less likely to achieve SVR compared to genotype 1 in univariate, but not in multivariate analysis.

Group-based trajectory modeling identified 6 distinct trajectories of GFR measures that best represented the GFR trajectories of patients following DAA treatment completion. Five trajectories demonstrated constant slopes over time, while only 1 trajectory (group 4) demonstrated declining GFR following DAA treatment. In this group, GFR decreased by a mean of 3.6 ml/min/1.73 m² from end of treatment to the 12–24 month endpoint, and by 13.1 ml/min/1.73 m² to the >24 month endpoint (Table 3). There was no statistically significant or clinically relevant change in GFR among the other trajectory groups.

The proportion of participants assigned to each group is presented in Table 4. Most participants were assigned to the non-chronic kidney disease group (Group 5) (54.0%) with an estimated GFR of 102 ml/min/1.73 m². Twenty seven percent of participants were assigned to the 2 groups with the lowest GFR (groups 1 and 2) – 11%, 12%, and 38% in groups 1, 2, and 3, respectively) compared to non-chronic kidney disease groups (67%, 33%, and 38% in groups 1, 2, and 3, respectively) compared to non-chronic kidney disease groups (11%, 12%, and 29% in groups 4, 5, and 6 respectively). The proportion of patients achieving SVR was high in all groups, ranging from 88% to 100%.
Table 2
Logistic regression analysis of baseline predictors of sustained virological response (n=431).

| Variable                                  | Simple model | Adjusted model |
|-------------------------------------------|--------------|----------------|
|                                           | OR 95%CI      | OR 95%CI        |
| Age                                       | 0.99 0.96–1.0| 0.98 0.92–1.0   |
| Female Sex                                | 1.0 0.94–2.0 | 1.3 0.51–3.1    |
| Diabetes                                  | 0.73 0.31–1.7| 0.73 0.24–2.2   |
| Cirrhosis                                 | 0.34 0.14–0.83*| 0.50 0.19–1.3 |
| HIV                                       | 0.34 0.12–0.96*| 0.71 0.17–3.4 |
| Sofosbuvir-based regimen                  | 0.60 0.18–2.0| 0.51 0.09–2.8   |
| Ribavirin                                 | 0.29 0.14–0.61*| 0.36 0.13–1.0 |
| GFR ≥90 ml/min/1.73 m²                    | Ref          | Ref             |
| GFR 60–89 ml/min/1.73 m²                  | 1.5 0.59–3.7 | 2.6 0.71–10.6  |
| GFR <60 ml/min/1.73 m²                    | 1.0 0.30–3.6 | 1.6 0.28–9.0   |
| Genotype                                  |              |                 |
| 1                                         | Ref          | Ref             |
| 2                                         | 0.85 0.19–3.9| 0.93 0.16–5.3   |
| 3                                         | 0.14 0.08–0.36| 0.32 0.10–1.0  |
| Other                                     | 0.26 0.09–0.78*| 0.23 0.06–0.86*|

Cirrhosis defined as transient elastography score >12.5 kPa.
Other genotype includes genotype 4 and mixed genotypes.
* denotes statistically significant at P<.05.
GFR = glomerular filtration rate.

Table 1
Characteristics of study participants by sustained virological response (SVR) status.

| Characteristic | All Treatments N=425 | SVR N=389 | Treatment Failures N=36 | P value |
|----------------|-----------------------|-----------|-------------------------|---------|
|                | N | % | N | % | N | % |         |         |
| Age            |   |   |   |   |   |   |         |         |
| Female sex     | 153 | 36 | 140 | 36 | 13 | 36 | .99     |         |
| Caucasian      | 332 | 81 | 307 | 82 | 25 | 69 | .08     |         |
| Genotype       | 1 |   | 309 | 73 | 293 | 75 | 16 | 44 | <.001 |
| 1a             | 164 | 56 | 155 | 56 | 9 | 69 |         |         |
| 1b             | 64 | 22 | 61 | 22 | 3 | 23 |         |         |
| 2              | 33 | 8 | 31 | 8 | 2 | 6 |         |         |
| 3              | 54 | 13 | 41 | 11 | 13 | 36 |         |         |
| 4              | 23 | 5 | 18 | 5 | 5 | 14 |         |         |
| Mixed          | 6 | 1 | 6 | 2 | — | — |         |         |
| Diabetes       | 65 | 15 | 58 | 15 | 7 | 19 | .47     |         |
| Fibrosis score | 1 |   | 80 | 22 | 76 | 22 | 4 | 16 | .13   |
| 2              | 61 | 17 | 59 | 17 | 2 | 8 |         |         |
| 3              | 48 | 13 | 47 | 14 | 1 | 4 |         |         |
| 4              | 177 | 48 | 159 | 47 | 18 | 72 |         |         |
| Transient Elastography score (kPa)* | 18.0 (15.3) | 17.4 (14.9) | 26.3 (18.0) | .01 |
| CAP (dB/m)     | 246 (51.5) | 246 (52.1) | 235 (37.2) | .33 |
| GFR (ml/min/1.73 m²)* | 94 (20.8) | 94 (21.0) | 95 (19.0) | .67 |
| GFR ≥90 ml/min/1.73 m² | 287 | 70 | 260 | 69 | 27 | 75 | .77 |
| GFR 60–89 ml/min/1.73 m² | 91 | 22 | 85 | 23 | 6 | 17 |         |         |
| GFR <60 ml/min/1.73 m² | 33 | 8 | 30 | 8 | 3 | 8 |         |         |
| ALT (IU/L)     | 99 (75.8) | 97 (76.1) | 112 (72.7) | .24 |
| AST (IU/L)     | 77 (52.3) | 74 (50.9) | 106 (67.8) | .003 |
| Viral load 10E6 | 3.3 (5.0) | 3.4 (5.1) | 2.7 (3.4) | .28 |
| Ribavirin      | 168 | 40 | 144 | 37 | 24 | 67 | .001 |
| Sofosbuvir-based regimen | 371 | 87 | 338 | 87 | 33 | 92 | .60 |
| HIV co-infection | 25 | 6 | 20 | 5 | 5 | 14 | .05     |         |

* Mean (SD).
Other genotype 1 subtypes (unspecified, n=62 and 1ab co-infection, n=2) not presented.
Valid percentages are presented.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, CAP = controlled attenuation parameter.
Multinomial logistic regression demonstrated that diabetes was associated with membership in group 1, group 2, group 3, and group 6 compared to group 5 (Table 5). Age also predicted group membership, with older age associated with groups with lower GFR. Cirrhosis predicted membership to group 6 (OR 9.5, 95% CI 1.1–81.2). Sex and SVR did not predict group membership.

4. Discussion

We evaluated the influence of DAA therapy on renal function following treatment completion in a large, real world cohort of HCV-infected patients. GFR remained constant during a 24-month time period following treatment among the majority of patients, including those with severe chronic kidney disease at treatment completion. SVR status did not predict post-treatment GFR or GFR trajectory following treatment. Existing evidence has demonstrated that SVR may reduce the incidence of endstage renal disease and chronic kidney disease, as demonstrated in cohorts including 293,480 participants\(^{[21]}\) and a 15-year follow-up period\(^{[22]}\) treated with interferon-based regimens. If SVR does slow the progression of renal disease, our findings indicate that this relative benefit may not be apparent until a number of years following treatment completion.

We found that baseline GFR did not predict SVR. While we did not analyze SVR in patients with severe renal impairment

Table 3

| Group | N | Proportion in Group | Baseline GFR | GFR | Age | Male | GT 1 | SVR | RBV | SOF | DM | Cirrhosis |
|-------|---|---------------------|--------------|-----|-----|------|------|-----|-----|-----|----|------------|
| 1     | 6 | 0.02                | 15 (5.2)     | 13  | 60  | 38   | 67   | 83  | 100 | 17  | 67 | 67         |
| 2     | 12| 0.04                | 40 (12.0)    | 42  | 61  | 8.3  | 50   | 42  | 100 | 67  | 92 | 33         |
| 3     | 24| 0.08                | 65 (12.5)    | 63  | 60  | 9.2  | 54   | 71  | 88  | 33  | 92 | 38         |
| 4     | 82| 0.02                | 85 (9.5)     | 85  | 60  | 8.0  | 62   | 77  | 99  | 45  | 87 | 11         |
| 5     | 160| 0.54                | 102 (6.4)    | 102 | 55  | 7.1  | 64   | 74  | 94  | 37  | 88 | 12         |
| 6     | 14| 0.05                | 124 (6.8)    | 125 | 59  | 12.5 | 71   | 36  | 93  | 71  | 71 | 29         |

Missing data: cirrhosis group 1 n = 1, group 2 n = 2, group 3 n = 3, group 4 n = 8, group 5 n = 13.

Glomerular filtration rate (GFR; ml/min/1.73 m\(^2\)) refers to the estimated post-treatment GFR from end of treatment to 6 months post-treatment predicted by the model (intercept value). Baseline GFR refers to mean baseline GFR from the data. Percentages are reported for male. Genotype 1 (GT 1).

The mean (SD) is reported for baseline GFR and age.

SVR = sustained virological response, RBV = Ribavirin, DM = diabetes mellitus, SOF = sofosbuvir included in treatment regimen and cirrhosis.
Cirrhosis

Treatment Failure

SVR. Prior to the introduction of DAAs, interferon-RBV therapy groups with lowest post-treatment GFR (group 1 and 2) achieved liver cirrhosis.[37]

The presence of resistance associated substitutions, or decompensated cirrhosis may demonstrate increased GFR and glomerular hypertrophy since this splanchnic vasodilatation is balanced by increased cardiac output.[42,43] Our finding may therefore reflect this state of hyperfiltration in compensated cirrhosis.

Our trajectory analysis demonstrated a decline in renal function in 1 quarter of our cohort. This decline was not associated with any of the predictor variables in multinomial regression analysis, including diabetes, cirrhosis, or SVR status. This reduction in renal function may therefore be attributable to age-related decline in GFR, as well as other etiologies of chronic renal disease that were not recorded in our study, such as hypertensive nephropathy or congenital renal disease.

Current guidelines recommend caution if considering initiating SOF-based therapy in patients with severe renal impairment, due to a theoretical risk of adverse events related to reduced renal excretion of SOF.[187] The Target 2.0 cohort study reports progressive deterioration of renal function in patients with severe renal impairment treated with SOF-containing regimens,[20] however other smaller studies have identified no adverse effect concerns with SOF treatment in patients with severe renal insufficiency.[17,19,44] The majority of participants in our cohort received SOF-based regimens, including those with severe renal impairment at baseline. Our observation that there was no decline in GFR in these patients suggests that SOF-based regimens are well-tolerated and do not influence renal function following treatment completion.

Our large cohort of HCV-infected patients were all treated at a single clinic. Selection bias was minimized by including all patients receiving interferon-free DAA therapy. Our population is representative of the general Canadian HCV population receiving treatment, as The Ottawa Hospital Viral Hepatitis Program follows over 4000 HCV patients from a catchment area including Eastern Ontario and Western Quebec, Canada. During the period of time considered in this analysis, provincial HCV DAA reimbursement was provided for patients with at least stage 2 fibrosis. Patients with decompensated cirrhosis were not funded. Some patients not qualifying for provincial reimbursement received treatment through private insurance, provincial special access, or pharmaceutical company compassionate release programs. These characteristics are reflected in our study population and should be considered with respect to the generalizability of our findings.

Certain limitations should be acknowledged. First, our retrospective observation period was limited to 24 months following treatment completion, which may have been insufficient to detect more gradual changes in renal function. Furthermore, confounding factors other than our measured variables may have reduced the validity of the obtained results. For example, it is feasible that improved engagement with health services per se could have facilitated initiation of renal-protective

| Variables          | OR     | 95% CI  | P value |
|--------------------|--------|---------|---------|
| Age                |        |         |         |
| Group 1: Age       | 1.1    | 0.92–1.3| .44     |
| Group 2: Age       | 1.1    | 1.0–1.3 | .01     |
| Group 3: Age       | 1.1    | 1.0–1.2 | .01     |
| Group 4: Age       | 1.1    | 1.1–1.2 | <.001   |
| Group 6: Age       | 0.77   | 0.69–0.87| <.001   |
| Sex                |        |         |         |
| Group 1: Female    | 0.62   | 0.06–5.9| .67     |
| Group 2: Female    | 2.3    | 0.60–3.2| .22     |
| Group 3: Female    | 1.9    | 0.69–5.0| .22     |
| Group 4: Female    | 1.1    | 0.60–2.1| .73     |
| Group 6: Female    | 0.46   | 0.09–2.4| .35     |
| Treatment Failure  |        |         |         |
| Group 1: Tx Failure| 0.34   | 0.02–5.4| .45     |
| Group 2: Tx Failure|        |         |         |
| Group 4: Tx Failure|        |         |         |
| Group 6: Tx Failure| 0.26   | 0.01–13.8| .50     |
| Diabetes           |        |         |         |
| Group 1: Diabetes  | 12.0   | 1.7–84.5| .01     |
| Group 2: Diabetes  | 4.1    | 0.95–17.3| .06    |
| Group 3: Diabetes  | 6.3    | 2.1–18.9| <.01    |
| Group 4: Diabetes  | 0.96   | 0.38–2.5| .96     |
| Group 6: Diabetes  | 15.0   | 2.4–94.3| <.01    |
| Cirrhosis          |        |         |         |
| Group 1: Cirrhosis | 0.75   | 0.11–5.3| .77     |
| Group 2: Cirrhosis | 5.7    | 0.67–48.4| .11    |
| Group 3: Cirrhosis | 0.58   | 0.21–1.6| .29     |
| Group 4: Cirrhosis | 0.74   | 0.40–1.4| .32     |
| Group 6: Cirrhosis | 9.5    | 1.1–81.2| .04     |

All groups were compared to group 5 as the reference. Odds ratio (OR) for treatment failure in groups 1, 2, 3, and 4 are not presented due to quasi-complete separation of data as all patients in these groups did not fail treatment.

Specifically, it is notable that all 18 patients assigned to the 2 groups with lowest post-treatment GFR (group 1 and 2) achieved SVR. Prior to the introduction of DAAs, interferon-RBV therapy was less efficacious in hemodialysis patients,[34] and the vast majority were not treated due to concerns regarding the adverse effects of RBV in endstage renal disease patients.[33] Our findings add further support to scarce existing evidence[36] that DAA-based regimens are similarly efficacious among patients with chronic kidney disease, including severe renal impairment (GFR < 30), compared to patients with normal renal function.

RBV treatment was a negative predictor of SVR in logistic regression analysis. This paradoxical result is likely due to a therapeutic channeling bias since RBV-containing regimens are more frequently selected in patients who are predicted to be difficult to cure due to factors that were not controlled for in our analysis. These factors include previous treatment failures, the presence of resistance associated substitutions, or decompensated liver cirrhosis.[37]

Our trajectory analysis demonstrated that diabetes status predicted membership to groups with decreased post-treatment renal function, but not to the trajectory with declining renal function. This is surprising given the significant incidence of diabetic nephropathy and GFR decline that has been demonstrated in general cohorts of patients with type 2 diabetes.[18–40] The stable GFR trajectories among diabetic patients in our cohort may represent a renal-protective effect of SVR. It is also possible that the magnitude of GFR decline among our cohort of participants, including those with diabetes, was not sufficient to be detected due to the relatively short follow-up period of 24 months. Small changes in GFR would also be difficult to detect due to the relative inaccuracy of GFR estimates in those without chronic kidney disease.[41]

In our study, baseline cirrhosis was predictive of membership to the trajectory group with the greatest mean post-treatment GFR (group 6). While end-stage cirrhosis is typically associated with reduced renal function due to splanchnic arterial vasodilatation, patients with compensated cirrhosis may demonstrate increased GFR and glomerular hypertrophy since this splanchnic vasodilatation is balanced by increased cardiac output.[42,43] Our finding may therefore reflect this state of hyperfiltration in compensated cirrhosis.

Our trajectory analysis demonstrated a decline in renal function in 1 quarter of our cohort. This decline was not associated with any of the predictor variables in multinomial regression analysis, including diabetes, cirrhosis, or SVR status. This reduction in renal function may therefore be attributable to age-related decline in GFR, as well as other etiologies of chronic renal disease that were not recorded in our study, such as hypertensive nephropathy or congenital renal disease.

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Certain limitations should be acknowledged. First, our retrospective observation period was limited to 24 months following treatment completion, which may have been insufficient to detect more gradual changes in renal function. Furthermore, confounding factors other than our measured variables may have reduced the validity of the obtained results. For example, it is feasible that improved engagement with health services per se could have facilitated initiation of renal-protective
interventions and medications that were not recorded in our study, such as angiotensin-converting enzyme inhibitors in diabetic patients. While using real-world clinical data adds to the generalizability of our findings, it may have also introduced bias by influencing which clinical data is collected. There may have been more available data for patients in whom there was a clinical rationale for certain laboratory measures, including GFR, leading to under-representation of normal values. However, it is notable that our group-based modeling methods allowed for complete data yielded GFR trajectories that closely resembled the original analysis (data not shown). Lastly, our renal function data was limited to eGFR as per the CKD-EPI equation. This approximation has been found to underestimate GFR, lacks sensitivity for detecting clinically significant changes in renal function among type-2 diabetic patients, as compared to iohexol plasma clearance. This may have led to underestimation of bias by in approximation has been found to underestimate GFR, lacks original analysis (data not shown). Lastly, our renal function data complete data yielded GFR trajectories that closely resembled the missing data, and a sensitivity analysis that only included notewas that our group-based modeling methods allowed for leading to under-representation of normal values. However, it is have been more available data for patients in whom there was a chronic kidney disease.

suggest that DAAs are safe and efficacious in the general population of HCV-infected patients, including patients with chronic kidney disease.

Author contributions
All authors made substantial contributions to the conception and design of the study. CG was responsible for data acquisition, MD, CC and CG provided analysis and interpretation. MD drafted the initial version of this manuscript and all authors provided feedback.

References
[1] Davis GL, Albright JE, Cook SF, et al. Projecting future complications of chronic hepatitis C in the United States. Liver Transp 2003;9:331–8.
[2] Sherman AC, Sherman KE. Extrapancreatic manifestations of hepatitis C infection: navigating CHASM. Curr HIV/AIDS Rep 2015;12:333–61.
[3] Fabrizi F, Verdecchia S, Messa P, et al. Hepatitis C virus infection increases the risk of developing chronic kidney disease: a systematic review and meta-analysis. Dig Dis Sci 2015;60:3801–13.
[4] Dalrymple IS, Koepsell T, Sampson J, et al. Hepatitis C virus infection and the prevalence of renal insufficiency. Clin J Am Soc Nephrol 2007;2:715–21.
[5] Li M, Wang P, Yang C, et al. A systematic review and meta-analysis: Does hepatitis C virus infection predispose to the development of chronic kidney disease? Oncotarget 2017;8:136/2.
[6] Fabrizi F, Pizzuti V, Messa P, et al. Impact of hepatitis C on survival in dialysis patients: a link with cardiovascular mortality? J Viral Hepat 2012; 19:601–7.
[7] Meyers CM, Seeff LB, Stehman-Breen CO, et al. Hepatitis C and renal disease: an update 1. Am J Kidney Dis 2003;42:631–57.
[8] Pockros PJ, Reddy KR, Mantry PS, et al. LO1: Safety of ombrabrevir/paritaprevir/ritonavir plus dasabuvir for treating HCV GT1 infection in patients with severe renal impairment or end-stage renal disease: The RUBY-I study. J Hepatol 2015;62:S257.
[9] Pockros PJ, Reddy KR, Mantry PS, et al. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. Gastroenterology 2016;150:1590–8.
[10] Muñoz-Gómez R, Rincón D, Ahumada A, et al. Therapy with ombrabrevir/paritaprevir/ritonavir plus dasabuvir is effective and safe for the treatment of genotypes 1 and 4 hepatitis C virus (HCV) infection in patients with severe renal impairment: a multicentre experience. J Viral Hepat 2017;24:464–71.
[11] Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet 2015;386:1537–45.
[12] Singh T, Gaurigus J, Anthony S, et al. Sofosbuvir-based treatment is safe and effective in patients with chronic hepatitis C infection and end stage renal disease: a case series. Liver Int 2016;36:802–6.
[13] Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. N Engl J Med 2017;377:1448–55.
[14] Koolslopi MP, Zhao W, Marbury TC, et al. Effects of Renal Impairment and Hemodialysis on the Pharmacokinetics and Safety of the Glecaprevir and PiBrentasvir Combination in Hepatitis C Virus-Negative Subjects. Antimicrob Agents Chemother 2018;62:e01990–17.
[15] KhatrI A, Dutta S, Marbury TC, et al. Pharmacokinetics and tolerability of anti-hepatitis C virus treatment with ombrabrevir, paritaprevir, ritonavir, with or without dasabuvir, in subjects with renal impairment. Clin Pharmacokinet 2017;56:133–63.
[16] Bhamidimarri K, Caul F, Peyton A, et al. Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of Hepatitis C in patients with end stage renal disease. J Hepatol 2015;63:763.
[17] Cox-North P, Hawkins KL, Rosseter ST, et al. Sofosbuvir-based regimens for the treatment of chronic hepatitis C in severe renal dysfunction. Hepatol Commun 2017;1:248–55.
[18] Gane EJ, Robson RA, Bonacini M, et al. Safety, anti-viral efficacy and pharmacokinetics (PK) of sofosbuvir (SOF) in patients with severe renal impairment. Hepatology 2014;60:667A.
[19] Hunderler GL, Sise ME, Wiscooky J, et al. Use of sofosbuvir-based direct-acting antiviral therapy for hepatitis C viral infection in patients with severe renal insufficiency. Infect Dis 2015;47:924–9.
[20] Saxena V, Koraishy FM, Sise ME, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis-C infected patients with impaired renal function. Liver Int 2016;36:807–16.
[21] Hsu Y-C, Ho HJ, Huang Y-T, et al. Association between antiviral treatment and extrarenal outcomes in patients with hepatitis C virus infection. Gut 2014;gutjnl-2014-308163.
[22] Arase Y, Suzuki F, Kawamura Y, et al. Development rate of chronic kidney disease in hepatitis C virus patients with advanced fibrosis after interferon therapy. Hepatol Res 2011;41:946–54.
[23] Fabrizi F, Donato FM, Messa P, Hepatitis C and Its Metabolic Complications in Kidney Disease. Ann Hepatol 2017;16;
[24] Feng B, Eknoyan G, Guo Z-s, et al. Effect of interferon-alpha-based antiviral therapy on hepatitis C virus-associated glomerulonephritis: a meta-analysis. Nephrol Dial Transplant 2011;26:640–6.
[25] Corogue M, Vallet-Pichard A, Pol S. HCV and the kidney. Liver Int 2016;36:328–33.
[26] Goetshir MR, Tamhane A, Varshney M, et al. Direct-acting antivirals in kidney transplant patients: successful hepatitis C treatment and short-term reduction in urinary protein/creatinine ratios. Pathog Immunity 2017;2:366.
[27] Sse ME, Bloom AK, Wiscooky J, et al. Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents. Hepatology 2016;63:408–17.
[28] Shimada M, Nakamura N, Endo T, et al. Daclatasvir/asunaprevir based direct-acting antiviral therapy ameliorates hepatitis C virus-associated cryoglobulinemic membranoproliferative glomerulonephritis: a case report. BMC Nephrol 2017;18:109.
[29] Mitchell T, Chakera A, Jeffrey GP, et al. Reversal of end-stage renal failure using direct-acting antiviral agents for chronic hepatitis C. Med J Aust 2016;205:205–6.
[30] Hogan JJ, Lim MA, Palmer MB, et al. Development of proteinuria and focal segmental glomerulosclerosis during direct-acting antiviral therapy for hepatitis C virus infection. Hepatology 2017;66:638–60.
[31] Ghosh M, Palmer MB, Najem CE, et al. New-onset hepatitis C virus-associated glomerulonephritis following sustained virologic response with direct-acting antiviral therapy. Clinical Nephrol 2017;87:261–6.
[32] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[33] Jones BL, Nagin DS. Advances in group-based trajectory modeling and an SAS procedure for estimating them. Sociol Methods Res 2007;35:542–71.

[34] Fabrizi F, Dixit V, Messa P, et al. Antiviral therapy (pegylated interferon and ribavirin) of hepatitis C in dialysis patients: meta-analysis of clinical studies. J Viral Hepatitis 2014;21:681–9.

[35] Goodkin DA, Bieber B, Gillespie B, et al. Hepatitis C infection is very rarely treated among hemodialysis patients. Am J Nephrol 2013;38:405–12.

[36] Cholongitas E, Pipili C, Papatheodoridis GV. Interferon-free regimens in patients with hepatitis C infection and renal dysfunction or kidney transplantation. World J Hepatol 2017;9:180.

[37] Chung RT, Ghany MG, Kim AY, et al. Hepatitis C Guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating Hepatitis C virus infection. Clin Infect Dis 2018;67:1477–92.

[38] Pavkov ME, Knowler WC, Lernley KV, et al. Early renal function decline in type 2 diabetes. Clin J Am Soc Nephrol 2012;7:78–84.

[39] De Cosmo S, Viazzi F, Pacilli A, et al. Predictors of chronic kidney disease in type 2 diabetes: a longitudinal study from the AMD Annals initiative. Medicine 2016;95:27.

[40] Zoppini G, Targher G, Chonchol M, et al. Predictors of estimated GFR decline in patients with type 2 diabetes and preserved kidney function. Clin J Am Soc Nephrol 2012;7:675–83.

[41] Stevens LA, Coresh J, Greene T, et al. Assessing kidney function—measured and estimated glomerular filtration rate. N Engl J Med 2006;354:2473–83.

[42] Wong F, Massie D, Colman J, et al. Glomerular hyperfiltration in patients with well-compensated alcoholic cirrhosis. Gastroenterology 1993;104:884–9.

[43] Hartleb M, Gutkowski K. Kidneys in chronic liver diseases. World J Gastroenterol 2012;18:3035.

[44] Li T, Qu Y, Guo Y, et al. Efficacy and safety of direct-acting antivirals-based antiviral therapies for hepatitis C virus patients with stage 4–5 chronic kidney disease: a meta-analysis. Liver Int 2017;37:974–81.

[45] Gaspari F, Ruggenenti P, Porrini E, et al. The GFR and GFR decline cannot be accurately estimated in type 2 diabetics. Kidney Int 2013;84:164–73.