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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology
**Manuscript NO:** 36557
**Title:** Impact of Sustained Virologic Response on Chronic Kidney Disease Progression in Hepatitis C
**Reviewer's code:** 02860875
**Reviewer's country:** United Kingdom
**Science editor:** Fang-Fang Ji
**Date sent for review:** 2017-10-06
**Date reviewed:** 2017-10-07
**Review time:** 1 Day

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ ] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ ] Grade B: Very good | [Y] Grade B: Minor language polishing | [ ] The same title | [ ] High priority for publication |
| [ ] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [Y] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [ ] Minor revision |
| [ ] Grade E: Poor | | [ ] No | [Y] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [ ] No | |

## COMMENTS TO AUTHORS

**The authors have used a large cohort of HCV-infected patients undergoing DAA treatment to ask if DAA treatment or treatment outcome impacts upon renal function. They have compared patients achieving and not-achieving SVR as well as comparing only the SVR group with a historical control cohort from the same centre. The written English and grammar is good, with only a few minor mistakes (eg manuscript p5, last line: ?improved renal function; simeprevir misspelled in figure 3).**

We thank the reviewer for these excellent comments. We provide answers to each of these comments and have modified our manuscript accordingly. The last line of page 5 was corrected to include 'improved' before 'renal function.' The spelling of simeprevir was corrected in figure 3.

**Major 1. Study group demographics. There are a few details missing from the demographics; I**

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**am assuming that patients who underwent transplantation during the 12 months after DAA treatment were excluded. Pertinent to renal function, there is no description in the current or historical cohorts of the rates of proteinuria or cryoglobulinaemia before, during or after DAA therapy. They at least acknowledge the issue of missing proteinuria in the discussion. How have they handled changes in demographics over time? For example one could hypothesise that failure to achieve SVR might be associated with worsening liver function, increased diuretic doses and declining renal function. Related to this, there is no description of liver function before, during or after treatment in any of the groups.**

We thank the reviewer for this comment. No patients underwent liver transplantation in the 12 months following DAA therapy. The rates of proteinuria and cryoglobulinemia were not included because this data is not available given that it was a retrospective review. It is noted in the discussion section that there is inadequate data on proteinuria. The data on renal function before and after DAA therapy is provided in the manuscript. Data was added to the manuscript to describe liver function at baseline by providing median MELD scores to better describe liver function in the patients with cirrhosis.

**2. Although the retrospective nature of the analysis limits the findings, could they not use the patients as their own controls? They say in the methods: 'Serum creatinine and estimated GFR was collected yearly for two consecutive years before and one year after treatment." If they calculated the change in eGFR from 1 year prior to DAA initiation (untreated) and compared it to change between DAA initiation to 1 year post-DAAs (treated) that might allow comparison of Delta-eGFR in the same patient.**

We thank the reviewer for this comment. We have calculated the change in eGFR 1-year prior to treatment and compared it to the eGFR 1-year following DAA therapy to allow comparison of Delta-eGFR in the same patient. We found that in patients who achieved SVR12, the decline in renal function was less following DAA therapy compared to prior. In patients who were treated and did not achieve SVR12, the decline in renal function was no different following DAA therapy compared to prior. This was added to the methods and results of our manuscript.

**3. Surely the most interesting implication of their findings is that DAA could have direct nephrotoxicity in addition to renal sparing effects when HCV is cleared. This is plausible and supported by differential changes in renal function with different regimens in figure. Should they not discuss this further?**

We thank the reviewer for this comment. In the discussion, we address that HCV clearance may have renal sparing effects, but DAAs could also have direct nephrotoxicity. There are no great published data that attributes kidney injury to DAA therapy. In patients treated with viekira or ledipasvir and sofosbuvir, there was a greater decline in eGFR in those who did not achieve SVR12 compared to those who achieved SVR12. However, the sample sizes for each treatment group are too small to make any definitive conclusions. This was added to the discussion.

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**Minor**

**1. Should the title be Chronic Kidney disease Progression?**

We thank the reviewer for this comment. The title was edited to “Impact of Sustained Virologic Response on Chronic Kidney Disease Progression in Hepatitis C.”

**2. Figure 1. The bars are labeled the wrong way round**

We thank the reviewer for this comment. The figure was corrected.

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**Reviewer's country:** Italy
**Science editor:** Fang-Fang Ji
**Date sent for review:** 2017-10-06
**Date reviewed:** 2017-10-17
**Review time:** 11 Days

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| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [ ] No | |

## COMMENTS TO AUTHORS

**This retrospective study have some limitations as underlined by the authors. This forces them to make speculations in order to explain the main result of the study, that is the lack of gain in eGFR decline in SVR compared with untreated patients. This is an issue undoubtedly useful for clinician, but already known.**

We thank the reviewer for these excellent comments. We provide answers to each of these comments and have modified our manuscript accordingly.

**Immune factors related with cryoglobulins may be one of the reason, but we need to consider the impact of the special population of veterans with older patients, male and highly prevalent**

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**comorbidities. A further comment on this issue should be desirable.**
We thank the reviewer for this comment. The veteran population is indeed a unique population with higher prevalence of CKD and it's associated co-morbidities. This was added to the discussion section.

**Unfortunately, patients with no response to DAA showed a worse renal function in the follow up than those untreated. The higher proportion of cirrhosis is one of the possible explanation. The impact of DAA regimen itself in this small number (38 patients) of highly prevalent cirrhotics is another possible cofactor, all the more considering that there is less comorbidity (other than cirrhosis).**
We thank the reviewer for this comment. Patients who were treated but did not achieve SVR12 had a greater decline in renal function compared to those who were untreated. The group of patients who were treated and did not achieve SVR12 did indeed have a higher proportion of cirrhosis, which may have contributed to their worsening renal function. This is included in the manuscript. There were no significant differences in DAA therapy between patients who achieved SVR12 and those who did not.

**A further table comparing non-responder to DAA with untreated, should be useful.**
We thank the reviewer for this comment. The data for patients who were treated with DAAs but did not achieve SVR12 is presented in table 1 and the data for patients who were not treated is presented in table 2 to allow for comparison between the two groups.

**Responses to the editor**

**Comment 1:**

Response: The postal code was added.

**Comment 2:**

Response: The postal code was added.

**Comment 3:**

Response: The grant approval statement was added as a PDF document.

**Comment 4:**

Response: The institutional review board statement was added as a PDF document.

**Comment 5:**

Response: The biostatistics review certificate was added as a PDF document.

**Comment 6:**

Response: The conflict of interest statement was addressed in the manuscript document and added as a PDF document stating that the authors have no conflicts to disclose.

**Comment 7:**

Response: The abstract was modified according to the guidelines set forth. The abstract length is greater than 246 words. The aim section is less than 20 words. The methods section is greater than 80 words. The results section is longer than 120 words and includes P values as appropriate. The conclusion section is less than 26 words and is written in the present tense.

**Comment 8:**

Response: An audio core tip was created and uploaded.

**Comment 9:**

Response: All reference numbers were changed from square brackets to superscripts

**Comment 10:**

Response: Article highlights were written and included.