## PEER REVIEW HISTORY



## ARTICLE DETAILS

| | |
|---|---|
| **TITLE (PROVISIONAL)** | Estimation of fibrosis progression rates for chronic hepatitis C: a systematic review and meta-analysis update |
| **AUTHORS** | Erman, Aysegul; Krahn, Murray; Hansen, Tawnya; Wong, Josephine; Bielecki, Joanna; Feld, Jordan; Wong, William; Grootendorst, Paul; Thein, Hla-Hla |

## VERSION 1 - REVIEW

| | |
|---|---|
| **REVIEWER** | Lise Lotte Gluud<br>Gastrounit<br>Denmark |
| **REVIEW RETURNED** | 13-Dec-2018 |

| | |
|---|---|
| **GENERAL COMMENTS** | The submitted paper entitled Estimation of fibrosis progression rates for chronic hepatitis C: a systematic review and meta-analysis update describes Markov Maximum Likelihood estimations of fibrosis progression based on a meta-analysis of 111 observational studies with 42,693 participants. The review is described as an update of a previous review published in 2008 including 111 observational studies with 33,121 participants. The updated review includes 45 studies not included in the original review.<br>The previous review found that the estimated annual mean stage-specific transition probabilities were: F0-->F1 0.117; F1-->F2 0.085; F2-->F3 0.120; and F3-->F4 0.116 (0.104-0.129). In the submitted review the stage-specific fibrosis progression rates were F0→F1: 0.107; F1→F2: 0.082; F2→F3: 0.117; F3→F4: 0.116.<br>I am impressed with the work that has gone into the paper. The searches are thorough and the selection criteria unbiased. The statistical methods are previously validated.<br>My main concerns are as listed below. I understand why the authors have chosen to submit a short paper. However, this means that important information can be lost. This makes the reading difficult.<br>1. The presented conclusions state that the review provides information and that it is a ‘’valuable resource for patients, clinicians and clinical policy makers’’. I would suggest that the authors should include an overall conclusion about the findings rather than simply stating that the results are important. Fibrosis progression rates are not intuitively easy to understand. Why, for example, do we see difference in rates between subgroups? Are the differences clinically important? In addition, it is important to |

| | |
|---|---|
| | (briefly) mention treatment vs non-treatment as we now have very safe and effective interventions for patients with hepatitis C.<br>2. The authors should clarify exactly where this paper adds to previous evidence; apart from the updated searches and inclusion of more recent trials with improved diagnostic methods, the overall results appear to be similar to the results of the previous review.<br>3. It is difficult to read the Prisma Flow chart. Some of the information about the search update may be included there. However, it would be very helpful if the text described the characteristics of the 45 studies which were excluded in the review update.<br>4. The review describes fibrosis progression rates and the text mentions that studies with a cross-sectional design are included. Please explain how progression rates can be estimated from a cross-sectional study?<br>5. The review includes a large number of studies, but apart from the overall design, I found no information about the quality of the evidence. This should be considered when making overall conclusions regarding the<br>The table of included studies mentions subgroups from studies (e.g., Liu 2014 – Marijuana [12] 10a and 10b). It is unclear why the studies are entered as subgroups. An Explanatory note would be helpful. Are any patients included in more than one?<br>The term non-clinical is difficult to understand. The authors mention screening as a non-clinical setting, but have included two relatively similar studies (Reggiardo 2012 [22] and Liu 2014 [8]) including a population described as 'blood transfusion'. One is classified as clinical and one as non-clinical. |

| | |
|---|---|
| **REVIEWER** | Antonio Facciorusso<br>University of Foggia<br>Italy |
| **REVIEW RETURNED** | 17-Dec-2018 |

| | |
|---|---|
| **GENERAL COMMENTS** | The manuscript is well written but several reviews/meta-analyses have been published in this field thus raising serious concerns on its novelty.<br>In particular a recent systematic review and meta-analysis led to similar results (although based on non-invasive fibrosis assessment):<br>-Singh S, Facciorusso A, Loomba R, Falck-Ytter YT. Magnitude and Kinetics of Decrease in Liver Stiffness After Antiviral Therapy in Patients With Chronic Hepatitis C: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018 Jan;16(1):27-38 |

| | |
|---|---|
| **REVIEWER** | Stephen Ryder<br>Nottingham University Hospitals NHS Trust<br>UK |
| **REVIEW RETURNED** | 29-Jan-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | I think the study provides a helpful update to the prior analysis. I have two areas which require further clarification.<br>The authors state that their previous manuscript included studies from 1990-2007 and this second analysis included those form 2007-2018. In the table of studies new to this analysis there are at least 3 which appear to be published before 2007. Were these |

| | |
|---|---|
| | missed in the initial analysis and included here because they have now been discovered or is there another explanation?<br>I have significant issues with the description of liver clinic populations v non-clinical populations. I don't think you mean non-clinical and this term is very confusing as even people who were detected in blood donor populations will have had a clinical assessment to establish a fibrosis stage. It seems to me that the real distinction is secondary care cohorts followed up in secondary care (which would include renal unit, HIV clinics) vs community screening such as blood donors. Clarity over the terms would help considerably in interpretation.<br>The cohorts are also somewhat confused with risk factor, for example in table 2 there are studies in "females". I assume this is really the Anti-D cohorts? It is actually more meaningful to look at those with more accurate dates of diagnosis and single exposure such as anti-D vs those with less certain dates of infection.<br>There is no overview of what marker of fibrosis was used and if this alters natural history, there may be significant differences in accuracy with differing techniques and at least some comment of which were used would be helpful. |

| | |
|---|---|
| **REVIEWER** | Ilias Gountas<br>National and Kapodistrian University of Athens, Athens, Greece |
| **REVIEW RETURNED** | 19-Apr-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | Comments to the authors<br>In this manuscript, the authors used a comprehensive systematic review to update and refine previous estimates concerning the progression of Hepatitis C (HCV). Although this team has published a very successful paper a decade ago, it is important to update such important estimates. An increasing number of countries are building their HCV elimination action plans based on mathematical modeling studies, thus the need for accurate HCV progression rates estimates is vital. Overall, the idea was clearly presented. The methodology of the statistical methods and analysis applied was appropriate, due to the experience of the team in this field. However, I believe there is still room for improvement, mostly in the discussion part, to make the manuscript more suitable for publication. Please see the detailed comments below:<br>• First, people who inject drugs (PWID) comprise one of the major transmission risk groups HCV. Previous estimates from other researchers (e.g. Smith et al. Int J Drug Policy. 2015) had estimated slower transition cirrhosis compared to this manuscript. The author should discuss the potential reasons for this difference in this population.<br>• Second, the authors should also justify why the most recent studies have estimated lower time to cirrhosis compared to older ones.<br>• Third, although I appreciate the comprehensive stratification by study population, I believe that some estimations may not so informative. For example, the confidence intervals of the progression rates for women is somewhat wide. Authors should discuss this.<br>• Minor change: Please update the first sentence of the manuscript. The last estimate regarding the global prevalence of HCV is about 1%. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Lise Lotte Gluud

Institution and Country: Gastrounit, Denmark

Please state any competing interests or state ‘None declared’: None declared

The submitted paper entitled Estimation of fibrosis progression rates for chronic hepatitis C: a systematic review and meta-analysis update describes Markov Maximum Likelihood estimations of fibrosis progression based on a meta-analysis of 111 observational studies with 42,693 participants. The review is described as an update of a previous review published in 2008, including 111 observational studies with 33,121 participants. The updated review includes 45 studies not included in the original review.

The previous review found that the estimated annual mean stage-specific transition probabilities were: F0-->F1 0.117; F1-->F2 0.085; F2-->F3 0.120; and F3-->F4 0.116 (0.104-0.129). In the submitted review the stage-specific fibrosis progression rates were F0→F1: 0.107; F1→F2: 0.082; F2→F3: 0.117; F3→F4: 0.116.

I am impressed with the work that has gone into the paper. The searches are thorough, and the selection criteria unbiased. The statistical methods are previously validated.

My main concerns are as listed below. I understand why the authors have chosen to submit a short paper. However, this means that important information can be lost. This makes reading difficult.

RESPONSE: We thank the reviewer for taking the time to review our manuscript and for helping to improve our study. We have submitted this paper as an original research paper. In the revised version, we have tried to elaborate on aspects of the study that the reviewers feel need more clarification. We hope that in the revised version, we were able to address these important issues.

1. The presented conclusions state that the review provides information and that it is a ‘’valuable resource for patients, clinicians, and clinical policymakers’’. I would suggest that the authors should include an overall conclusion about the findings rather than simply stating that the results are important. Fibrosis progression rates are not intuitively easy to understand. Why, for example, do we see a difference in rates between subgroups? Are the differences clinically important? In addition, it is important to (briefly) mention treatment vs. non-treatment as we now have very safe and effective interventions for patients with hepatitis C.

RESPONSE: We thank the reviewer for taking the time to carefully evaluate our work. The purpose of our study is to provide estimates of fibrosis progression in untreated individuals for clinically important CHC subpopulations. We agree that FPRs may not be intuitive. Because of this, we have translated these estimates into more intuitive time-to-cirrhosis estimates.

As per the reviewer's suggestion, we have made additions to our discussion section to highlight some of these differences in time-to-cirrhosis so as to provide a better overall description of findings [please see PAGES 15; PARAGRAPH 1] as follows:

"To help describe the differences in disease progression across the different groups, our updated analysis used the covariate-adjusted stage-specific fibrosis progression rates to estimate the average expected time-to-cirrhosis for each group. After adjustment for confounders, we found that time-to-cirrhosis was 43 years for genotype-1 vs. 34 years for genotype-3 groups. In general, adjusted progressions were slower for the blood donors (55 years), females (52 years), Black patients (46 years) and generally faster for IDUs (40 years), infectious diseases units and community patients (~34 years) and Asian populations (29 years). "

We thank the reviewer for this suggestion and feel that this has been a helpful way to summarize the large amount of prognostic information that we have generated in this review.

Regarding the reviewer's final point, we only included untreated individuals in the current analysis. We also agree that given the availability of highly effective therapies estimates of the natural history of fibrosis progression among untreated individuals is perhaps not as useful in the clinical context. However, please note that these estimates of "baseline progression" are still necessary for modeling studies, including health economic models. Therefore, prognostic estimates (especially for clinically important subpopulations, e.g., people who inject drugs, liver clinic populations, pediatric pts, etc.) provided here are still important for clinical policy models. Furthermore, given the upcoming elimination efforts as set forth by the WHO, modeling studies of HCV are now increasingly important to help inform policy.

2. The authors should clarify exactly where this paper adds to previous evidence; apart from the updated searches and inclusion of more recent trials with improved diagnostic methods, the overall results appear to be similar to the results of the previous review.

RESPONSE: We thank the reviewer. Please note that this update was undertaken at the request of CADTH (Canadian Agency for Drug Technologies in Health) to derive updated estimates of prognosis, as our previous estimates, having been derived a decade ago, were extremely outdated, and as systematic reviews need to be kept current to inform policy. However, we also agree with the reviewer that our overall findings are not substantially different from the original results. Nevertheless, we feel that our study's findings mainly highlight important issues around heterogeneity that have not been explored or discussed in as much detail in the original study.

As per the reviewer's suggestion, in the revised manuscript, we have made several modifications to our discussion section in order to provide a more detailed comparison of our results to previous work [please see PAGE: 14-16].

3. It is difficult to read the Prisma Flow chart. Some of the information about the search update may be included there. However, it would be very helpful if the text described the characteristics of the 45 studies which were excluded in the review update.

RESPONSE: Thank you. A description of the excluded studies has now been added. These additions have been described on PAGE 10; PARAGRAPH 2. Also, please see S5 Table in the Supplement for more information on the excluded studies.

Finally, please note that S3 and S4 Tables in the Supplement also report the characteristics for each study identified by our systematic review. These tables include data on both the studies included in the meta-analysis and those excluded from the meta-analysis due to incomplete HCV RNA data.

4. The review describes fibrosis progression rates, and the text mentions that studies with a cross-sectional design are included. Please explain how progression rates can be estimated from a cross-sectional study?

RESPONSE: Fibrosis progression rates can be estimated from any study where the estimated mean duration of infection and the distribution of fibrosis scores have been reported, and this does not necessitate a prospective design. Because of this, we are able to generate estimates from cross-sectional/retrospective studies (as well as prospective-retrospective studies).

Traditionally, prognostic studies of CHC employ two main methods to estimate FPRs: 1) a direct method, involving serial liver biopsies and the time elapsed between them (thus, either a prospective or longitudinal assessment); and 2) an indirect method, involving a single biopsy and the estimated duration of HCV infection (e.g., cross-sectional data).

- in method 1, if an individual has a fibrosis stage of F2 at the initial assessment and progresses to F3 at the subsequent assessment, which is performed seven years later, then the FPR would be estimated as (3-2)/7=0.143 fibrosis units/year.

- In method 2, if an individual only has a single assessment of fibrosis, indicating, for example, a fibrosis stage of F2, and an estimated duration of infection of 15 years at the time of this assessment, and if we assume that fibrosis stage at the onset of infection was F0, then FPR would be estimated as follows:

(2-0)/15=0.133 fibrosis units/year.

Although the direct method is helpful in evaluating the variation in FPRs across different fibrosis stages, this method is less common and tends to involve patients who need to be monitored more closely for disease progression. The more common indirect method assumes that patients have no evidence of fibrosis (i.e., F0) at the onset of infection, and that liver disease progression occurs at a

constant rate from HCV acquisition to the time of histological assessment; however, evidence suggests that fibrosis progression may be nonlinear with a slower progression between the earlier stages and a faster progression later on.

To overcome some of the drawbacks associated with the earlier methods, an alternative model-based approach, the Markov Maximum Likelihood Estimation method (MMLE), was developed by our group in 2004 (Yi et al., 2004, https://doi.org/10.1046/j.1365-2893.2003.00484.x ). This method allows for the estimation of stage-specific FPRs from data sources that involve only a single liver biopsy, thus allowing for a larger body of evidence from potentially less biased studies to help inform prognosis. Therefore, our analysis includes cross-sectional and other study designs. However, please note that we also stratify our analysis by study design to evaluate the impact of differences in study conduct on estimates.

5. The review includes a large number of studies, but apart from the overall design, I found no information about the quality of the evidence. This should be considered when making overall conclusions regarding the

RESPONSE: We thank the reviewer. We certainly agree that quality appraisal is an important component of evidence synthesis. Regarding this issue, please see comments to the editor above.

6. The table of included studies mentions subgroups from studies (e.g., Liu 2014 – Marijuana [12] 10a and 10b). It is unclear why the studies are entered as subgroups. An Explanatory note would be helpful. Are any patients included in more than one?

RESPONSE: We thank the reviewer. Please note that patients were not double counted across the different groups. Studies that reported results in subgroups, which may influence disease progression were entered separately in our analysis. An explanatory note has been added to the revised study as per the reviewer's suggestion [PAGE 7; PARAGRAPH: 4] as follows:

"Studies that reported results in subgroups, which may influence disease progression, were extracted separately."

Additionally, notes were also added to the supplement [SUPPLEMENT PAGE: 41]

7. The term non-clinical is difficult to understand. The authors mention screening as a non-clinical setting,but have included two relatively similar studies (Reggiardo 2012 [22] and Liu 2014 [8]) including a population described as 'blood transfusion.' One is classified as clinical and one as non-clinical.

RESPONSE: We thank the reviewer, and we also agree that this terminology may be confusing. However, to prevent any misinterpretation, we had provided a list of descriptions/definitions of all terms, which were used to categorize the included studies by the two independent reviewers.

This information has been provided on the S1 Table in the Supplement. First, please note that the "setting" refers to the setting where the infected individuals were first identified.

- Therefore, in our study, the term "Non-clinical" would apply to patients who were identified in a "non-clinical setting" though screening-efforts such as community/population screening programs, etc. For example, patients initially identified at a "blood donation center or regional center." Therefore, this group typically would include more asymptomatic individuals (vs. those identified at a clinical setting).

- In contrast, "clinical" setting refers to: "Individuals who were identified and/or assessed for their HCV status and liver disease in a clinical/tertiary care setting" Therefore, this group generally includes patients who receive an HCV diagnosis following the development of symptoms related to CHC.

However, please note that patients in both groups (those identified in either in a non-clinical or a clinical setting) will eventually go on to receive further testing including fibrosis assessment, etc., usually in a clinical setting (as also indicated by Reviewer 3).

Based on the comments from both Reviewer 1 and Reviewer 3, we have tried to improve clarity around the study setting definition. We have made small modifications to the results section to highlight that the setting refers to where patients are initially identified [please see PAGE:11; PARAGRAPH: 3]

With respect to the issue of blood transfusion, this refers to the mode of infection. Although the mode of infection (i.e., blood transfusion, blood donor, injection drug use, sporadic) could be related to the setting in which patients are identified (i.e., through screening efforts focusing on groups), this is not always the case. Please note that not all individuals who have acquired HCV through blood transfusion necessarily are identified through screening efforts. Through, sometimes this is difficult to establish from the published information. This also another reason why we also additionally stratified our analysis by mode of infection as well.

Reviewer: 2

Reviewer Name: Antonio Facciorusso

Institution and Country: University of Foggia, Italy

Please state any competing interests or state ‘None declared’: None declared

The manuscript is well written but several reviews/meta-analyses have been published in this field thus raising serious concerns on its novelty.

In particular a recent systematic review and meta-analysis led to similar results (although based on non-invasive fibrosis assessment):

-Singh S, Facciorusso A, Loomba R, Falck-Ytter YT. Magnitude and Kinetics of Decrease in Liver Stiffness After Antiviral Therapy in Patients With Chronic Hepatitis C: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018 Jan;16(1):27-38

RESPONSE: We thank the reviewer for highlighting related studies. However, please note that our research question is very different from the study highlighted by the reviewer.

Firstly, our review estimates the natural history of HCV (i.e., fibrosis progression in untreated individuals), while Sing et al. have evaluated the effect of anti-viral treatment on liver stiffness.

Second, this review has also not generated FPRs (i.e., progression rates) but has instead reported only the mean changes in liver stiffness measurements post-antiviral therapy.

Although, we agree that this is useful information in the era of DAAs, our intent in the enclosed study was to derive the fibrosis progression rates (FPRs) among untreated individuals, as these estimates provide necessary data on the expected “baseline” disease progression among individuals with CHC, which is required for modeling studies of HCV (e.g., economic models, cost-effectiveness studies, decision-analysis models, etc.). The estimates generated by Sing et al., though useful, would not be as relevant or directly useful for this purpose.

Reviewer: 3

Reviewer Name: Stephen Ryder

Institution and Country: Nottingham University Hospitals NHS Trust, UK

Please state any competing interests or state ‘None declared’: none

I think the study provides a helpful update to the prior analysis. I have two areas which require further clarification.

RESPONSE: We thank the reviewer for taking the time to carefully read our work. We hope that we were able to address the reviewer’s concerns in the enclosed revisions and responses.

1. The authors state that their previous manuscript included studies from 1990-2007, and this second analysis included those form 2007-2018. In the table of studies new to this analysis, there are at least 3, which appear to be published before 2007. Were these missed in the initial analysis and included here because they have now been discovered, or is there another explanation?

RESPONSE: We thank the reviewer for carefully examining our review. The reviewer is correct. Because this is a systematic review update, we include any studies that may have been missed in the original search performed a decade ago, in 2007. Some of these studies have been identified by through the use of overlapping search periods (between the original search and the updated search), or through supplemental searches (citation and references of other published reviews).

2. I have significant issues with the description of liver clinic populations v non-clinical populations. I don't think you mean non-clinical and this term is very confusing as even people who were detected in blood donor populations will have had a clinical assessment to establish a fibrosis stage. It seems to me that the real distinction is secondary care cohorts followed up in secondary care (which would include renal unit, HIV clinics) vs. community screening such as blood donors. Clarity over the terms would help considerably in interpretation.

RESPONSE: Thank you. Please see the response to Reviewer 1 Question 7 for further clarification.

3. The cohorts are also somewhat confused with risk factor; for example, in table 2, there are studies in "females." I assume this is really the Anti-D cohorts? It is actually more meaningful to look at those with more accurate dates of diagnosis and single exposure such as anti-D vs. those with less certain dates of infection.

RESPONSE: We thank the reviewer. We also agree that accurate information on the date/duration of infection is necessary for generating reliable estimates of prognosis. This is an inherent limitation for most prognostic studies of CHC and has been discussed in our limitations section as well [PAGE: 15;

PARAGRAPH:2]. However, we feel that the reviewer's suggestion would substantially restrict our analysis and reduce its utility for several reasons:

1. There are not very many studies that report an accurate date of infection for all subjects.

2. Restricting the analysis to cohorts with a more accurate date of infection would substantially reduce generalizability.

3. Moreover, it is essential to understand the natural history and to estimate prognosis for clinically important groups such as people who inject drugs (or, PWIDs) – despite a generally less accurate date of injection for this population.

4. Therefore, instead of restricting the analysis in such a strict away, we have chosen to stratify studies by multiple factors including, for example, the mode of infection, which is a factor related to the issues of exposure date.

4. There is no overview of what marker of fibrosis was used, and if this alters natural history, there may be significant differences in accuracy with differing techniques and at least some comment of which were used would be helpful.

RESPONSE: Thank you. We agree as well. However, please note that a great majority (93%) of studies included in our review used a liver biopsy to detect fibrosis. Because only a few studies have used methods other than biopsy, the assessment method has no impact on our overall findings.

However, we agree that this is an important point and we have made modifications to our results section to provide more detail on this issue [please see PAGE: 10 PARAGRAPH: 3] as follows:

"Majority of study groups (124 out of 131) assessed hepatic fibrosis using only histology; only 7 performed a non-invasive assessment of hepatic fibrosis (6 used LSM and 1 used a combination of invasive and non-invasive methods)."

Further, S3Table in the Supplement (in the last column of the table) also describes the "assessment method" (e.g., LB; LSM; etc.) for each study; while S2Table in the Supplement describes the criteria used to convert various commonly used invasive and non-invasive scoring systems to the well-validated METAVIR system (along with the associated AUROC estimates).

Finally, although we also agree with the reviewer regarding the issue of diagnostic accuracy, unfortunately, diagnostic accuracy is also an inherent issue for liver biopsies as well, which have a greater tendency for inter and intra-observer variability vs. non-invasive assessment methods.

Reviewer: 4

Reviewer Name: Ilias Gountas

Institution and Country: National and Kapodistrian University of Athens, Athens, Greece

Please state any competing interests or state ‘None declared’: None declared

Comments to the authors

In this manuscript, the authors used a comprehensive systematic review to update and refine previous estimates concerning the progression of Hepatitis C (HCV). Although this team has published a very successful paper a decade ago, it is important to update such important estimates. An increasing number of countries are building their HCV elimination action plans based on mathematical modeling studies, thus the need for accurate HCV progression rates estimates is vital. Overall, the idea was clearly presented. The methodology of the statistical methods and analysis applied was appropriate, due to the experience of the team in this field. However, I believe there is still room for improvement, mostly in the discussion part, to make the manuscript more suitable for publication. Please see the detailed comments below:

RESPONSE: We thank the reviewer taking the time to carefully assess our results. We hope that we were able to address the reviewer’s concerns in the revised manuscript and the responses provided below.

1. First, people who inject drugs (PWID) comprise one of the major transmission risk groups HCV. Previous estimates from other researchers (e.g. Smith et al. Int J Drug Policy. 2015) had estimated slower transition cirrhosis compared to this manuscript. The author should discuss the potential reasons for this difference in this population.

RESPONSE: We thank the reviewer. We also agree that this merits further discussion. As per the reviewer’s suggestion, we have made additions to our discussion section [please see PAGE: 14; PARAGRAPH: 2] as follows:

“With respect to the IDU population, based on the 10 groups identified, we found a faster average time-to-cirrhosis for this population (37 years), when compared to our earlier estimate (40 years), and to a previous review, which used similar methods (46 years) [29]. Following covariate adjustments, the progression was slightly slower (40 years); this could be due to the inclusion of more genotype-3 infected individuals in the present study.”

2. Second, the authors should also justify why the most recent studies have estimated lower time to cirrhosis compared to older ones.

RESPONSE: We thank the reviewer. As per the reviewer's suggestion, we have modified our discussion to provide some plausible explanations for these findings [please see PAGE: 14; PARAGRAPH: 1] as follows:

"…This is possibly because the updated review included more studies where patients were identified through screening efforts in non-clinical settings, and thus involved less symptomatic patients when compared to the original study."

3. Third, although I appreciate the comprehensive stratification by study population, I believe that some estimations may not so informative. For example, the confidence intervals of the progression rates for women is somewhat wide. Authors should discuss this.

RESPONSE: We thank the reviewer for carefully evaluating our results. In general, the size of the confidence interval in a meta-analysis depends on 1) the precision of the study estimates, which is related to the size of the study, and 2) the number of studies included in the meta-analysis. Because of this, we would expect subgroups that include a small number of studies and/or a small number of study subjects to generate wider confidence intervals. Moreover, in random-effects meta-analyses (as is the case here) confidence intervals tend to be wider (vs. fixed effects models) and the CIs also tend to widen further with increasing heterogeneity. Therefore, in random-effect models, if the addition of more studies results in an increase in heterogeneity (or, results in an increase in the extent of between-study variability), this may actually also widen the confidence intervals. Thus, the extent of the confidence intervals seen across the various subgroups likely depend on these three factors (i.e., the study size, the number of included studies, and the extent of heterogeneity across the studies included in the groups).

A brief explanatory note has now been added to the revised document [Please see PAGE 22; TABLE 2] as follows:

"…the size of CIs of each subgroup depends on the N. of studies, study size, and the extent of heterogeneity across the studies included in the subgroup."

4. Minor change: Please update the first sentence of the manuscript. The last estimate regarding the global prevalence of HCV is about 1%.

RESPONSE: Thank you. We also agree. The changes have been made to the introduction with updated citations [please see PAGE 5; PARAGRAPH 1] as follows:

"An estimated ~1% of the world's population is infected with the Hepatitis C virus (HCV) [1,2]."

## VERSION 2 – REVIEW

| | |
|---|---|
| **REVIEWER** | Lise Gluud<br>Gastrounit<br>Copenhagen University Hospital Hvidovre<br>Denmark |
| **REVIEW RETURNED** | 26-Jun-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | This work that has gone into this review is impressive<br>I have no additional comments |

| | |
|---|---|
| **REVIEWER** | Stephen Ryder<br>Nottingham University Hospitals NHS trust |
| **REVIEW RETURNED** | 11-Jun-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | My initial comments have been addressed very thoroughly and I think the manuscript improved in clarity and focus. I understand the response over defined dates of infection vs not although I still do not necessarily agree I think the authors provide adequate data in all other respects now so I will not push the point! |

| | |
|---|---|
| **REVIEWER** | Ilias Gountas<br>National and Kapodistrian University of Athens, Athens, Greece |
| **REVIEW RETURNED** | 29-Jun-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thank you for addressing all of my comments. |