

Dear Editor,

We hereby submit a revised version of a Research Letter entitled “Persistent elevation of fibrosis biomarker Cartilage Oligomeric Matrix Protein following HCV eradication“. The ms was previously submitted to World Journal of Gastroenterology (Manuscript number 45667). We have now revised the manuscript in accordance with the reviewers’ comments, the specific instructions received from the editorial office as well instructions to authors from World Journal of Hepatology.

PDF-copies of the approved grant application forms have been uploaded. An audio file of the final core tip has now been included. The original editable ppt-file for Figure 1 has now been separately uploaded.

We sincerely appreciate the opportunity to submit a revised version of our manuscript to World Journal of Hepatology. We also appreciate the thorough review by the 4 referees on our manuscript. Please find attached our response to their comments. In the updated manuscript, all changes have been marked in yellow.

On behalf of all the co-authors,

Kristofer Andréasson

MS 45667: Persistent elevation of fibrosis biomarker Cartilage Oligomeric Matrix Protein following HCV eradication

Response to reviewers' comments

Reviewer 1 (02539326)

The authors investigated the possible role of S-COMP as biomarker for hepatic fibrosis and HCC after successful therapy of CHC with DAA.

We appreciate the reviewer's summary, evaluation and conclusion (*Accept*) of our manuscript.

Comment 1.

The study is interesting, but the number of patients is too low to draw definitive conclusions. As the authors assessed, data need to be enlarged to better understand the real utility of this marker in the follow-up of patients with SVR after DAA treatment.

We are thankful for the opportunity to respond to the reviewer's comment. Indeed the number of patients included is a limitation of this study. Still, we were able to reproduce previous results, namely;

- S-COMP was higher in HCV-patients with liver cirrhosis (13 vs 9.0 U/l; $p=0.036$)
- Successful HCV-treatment was associated with normalization of both the APRI (from 0.62 to 0.29; $p<0.001$) and liver elasticity (from 8.3 to 5.4 kPa; $p<0.001$).

We have also added the following sentence in the manuscript (line 147):

“Further studies encompassing a larger number of patients are needed.”

Reviewer 2 (02445854)

This is a well written report. I don't have any criticism to it.

We appreciate the reviewer's evaluation and conclusion (*Accept*) of our manuscript.

Reviewer 3 (03476715)

In this preliminary study, Kristofer et al. aimed to found the clinical significance of S-COMP in HCV patients. The results showed that S-COMP levels were higher in transient elastography-proved cirrhosis, however, this biomarker did not significantly decreased with the improvements of liver function test and liver elasticity. It is an interesting study, but there are some major issues needs to be addressed.

We appreciate the reviewer's evaluation and conclusion (*Major revision*) of our manuscript and are grateful for the opportunity to respond to the reviewer's comments.

Comment 1

"Page 4 Line 115. "One patient developed HCC prior to the inclusion in this study. This patient exhibited the highest (21 U/L) level of S-COMP in this study." This study did not exclude patients with HCC, which had been proven to have a higher COMP level. I would like to see the results after this particular patient was excluded from final analysis."

On the advice of the reviewer, we have excluded the patient who developed HCC. Below is the result-section with novel data inserted in yellow, based on statistical analysis of only 37 subjects, the HCC patient excluded.

...Baseline median (IQR) age, viral levels and liver stiffness were 58 (43 – 63) 58 (41 – 63) years, 2.0×10^6 (9.7×10^5 – 4.7×10^6) 1.9×10^6 (9.7×10^5 – 4.3×10^6) and 8.3 (6.9 – 11.1) 8.4 (7.0 – 11.1) kPa, respectively.

Six patients had a TE measurement indicating liver cirrhosis at baseline. These subjects had higher AST to platelet ratio index (APRI)-scores and S-COMP levels compared to the other patients (0.91 vs 0.55; $p=0.008$ 0.91 vs 0.50; $p=0.008$ and 13 vs 9 U/l; $p=0.036$ 13 vs 9 U/l; $p=0.026$, respectively). Median (IQR) treatment duration was 84 (60 – 95) 84 (60 – 96) days, and all study participants reached SVR. TE was performed at baseline and at follow up, 517 (468 – 639) 531 (466 – 640) days later. Liver stiffness decreased significantly during this period (from 8.3 (6.9 – 11.1) to 5.4 (4.4 – 6.6) kPa; $p<0.001$ 8.4 (7.0 – 11.1) to 5.5 (4.4 – 6.7) kPa; $p<0.001$; Figure 1A). Also, APRI decreased significantly, from 0.62 to 0.29 ; $p<0.001$ 0.62 – 0.29; $p<0.001$, Figure 1B. In contrast, S-COMP levels did not decrease from baseline 9.5 (8 – 13) versus 10.5 (9.8-13) U/L at

follow up; $p=0.14$ 9 (8.0 – 13) versus 10 (9.5 – 13) U/L at follow up; $p=0.19$. Similar levels of S-COMP were measured at 4 weeks of treatment 9.0 (8 – 12) 9.0 (8.0 - 12) and at end of treatment 10 (6.8 – 12) 10 (6.5 – 13) U/L (Figure 1C). Furthermore, changes in S-COMP over time was not associated with any disease characteristics (data not shown).

There was a significant relationship between baseline S-COMP and viral levels ($r_s=0.45$, $p=0.005$) ($r_s=0.41$, $p=0.012$) at baseline.”

In respect to the predefined inclusion criteria for this study, we want to include the patient with HCC. In the updated manuscript we have therefore chosen **not** to exclude this patient.

Comment 2

“Since COMP is a molecule in fibrotised tissues, I would like to see if there is any difference between the COMP and the other classic fibrotic markers(for example, Hyaluronic Acid,Collagen Hydrogel) in the same population.”

We agree with the reviewer that it would be informative to analyse S-COMP in relation to other fibrotic biomarkers. Unfortunately this was not done, and it is not possible to do retrospectively in this cohort. We have added the following sentence, line 147.

“Further studies encompassing a larger number of patients are needed. In such studies, S-COMP should ideally be compared with other fibrotic biomarkers such as hyaluronic acid.”

Comment 3

Page 2 Line 35 “This is of interest since these patients are still at risk of developing hepatocellular carcinoma, and COMP has been presented as a biomarker of carcinoma development”. I think this sentence is not propriate as the results of this study did not provide any evidence of HCC development in the follow up”

The above mentioned sentence has been removed in the revised version in the manuscript.

Reviewer 4 (00053659)

Andr ásson et al. wrote a letter to the editor regarding serum levels of fibrosis biomarker Cartilage Oligomeric Matrix Protein in CHC patient.

We appreciate the reviewer's conclusion on our manuscript (*Major revision*).

Comment 1

It is interesting, but the paper what they cited and discussed about it was a different journal, unfortunately. Furthermore, the most description seemed to be original results from an unpublished study. I recommend you to submit this letter after accepting your study to world journal of gastroenterology. Alternatively, you should consider it to submit world journal of hepatology.

Our original version of this Letter was submitted to World Journal of Gastroenterology after reading the author instructions for that journal. In response to the reviewer and the Editor-in-Chief, the revised version is submitted to World Journal of Hepatology. It contains original data on S-COMP that has not, and will not be published elsewhere. To our knowledge, it is the first prospective analysis of S-COMP in chronic liver disease.