Author’s response to reviews

Title: Three-dimensional CT texture analysis of anatomic liver segments can differentiate between low-grade and high-grade fibrosis

Authors:

Bettina Katalin Budai (bettinabudai.95@gmail.com)
Ambrus Tóth (tothambrusch@gmail.com)
Petra Borsos (petraborsos96@gmail.com)
Veronica Grace Frank (veronicafrank987@gmail.com)
Sonaz Shariati (sunny.shariati@gmail.com)
Bence Fejér (bence.fejer@gmail.com)
Anikó Folhoffer (folhoffer@gmail.com)
Ferenc Szalay (szalay.ferenc@med.semmelweis-univ.hu)
Viktor Bérczi (berczi@hotmail.com)
Pál Novák Kaposi (kaposipal@gmail.com)

Version: 1 Date: 02 Jul 2020

Author’s response to reviews:

To: Prof. Timm Denecke
associate editor
BMC Medical Imaging

2nd July 2020

Dear Professor Denecke,

Thank you very much for your expert comments on our paper BMIM-D-20-00188 titled: "Three-dimensional CT texture analysis of anatomic liver segments can differentiate between low-grade and high-grade fibrosis". We provide detailed answers to all the reviewers' comments as listed below and also modified the manuscript's text and figures accordingly. The formatting of a cited article (No.10.) was also corrected in the References section. We hope that our answers will be satisfactory to you. Please, let us know if any further clarification is needed!
# Reviewer 1:

Thank you for letting me review the present article titled "Three-dimensional CT texture analysis of anatomic liver segments can differentiate between low-grade and high-grade fibrosis." In the present study, the author evaluated the efficacy of 3D texture analysis in differentiate between low-grade and high-grade liver fibrosis. Generally, the study seems to be well conducted, although Materials and Methods section needs to be more clarified so that we can judge the scientific correctness of the study. Also, the author should respond to the major points listed below.

**Major point**

1. In this study, texture features from each liver segment are used to train machine learning, and the result is evaluated by a segment basis only. Although, what we want to know is that if the patients have high-grade liver fibrosis or not. So, the patient's basis analysis is essential. Also, how should we judge if the result differed by segments in a single patient?

**Answer 1:**

We thank the reviewer for drawing attention to the potential clinical applications of our CTTA based model. The patient-based analysis can be performed by the prediction of either the whole liver segment or the right lobe, which is measured during shear wave elastography. When we predicted these two segments with the pre-trained machine learning models the cross-validated accuracy of the RFC model was better in the right lobe 0.812 95% CI: 0.645-0.979 than in the whole liver 0.705 95% CI: 0.52-0.884. Meanwhile, the SVM model had lower, but similar prediction accuracy in both the right lobe 0.67 95% CI: 0.556 - 0.784 and the whole liver 0.695 95% CI: 0.636 - 0.754 segments. Based on this analysis we can suggest that the RFC model should be applied to texture features extracted from the right lobe when the fibrosis status of an individual patient is evaluated. This analysis is now included in the revised manuscript (please see page 13). However, we should emphasize that the models' accuracy to predict a single segment can be improved if the training is conducted on a dataset, which consists of the same segments only. To achieve this goal the number of patients must be significantly increased in the training dataset, which is out of the scope of the present study. Meanwhile, the 81% AUC is still comparable with other studies, which reported similar classification rates with CTTA. This is now discussed in the manuscript (please see page 18).

2. In the background section, the author wrote that they aimed to develop CTTA based prediction models "irrespective of variations in scanning parameters." In the present study, two CT scanners are used, and their reconstruction algorithms differ. Although the result is not shown by a CT scanner basis, so we cannot evaluate if the gained model has the same diagnostic accuracy in both scanners evaluated in this study. This should be assessed since it is well known that CT reconstruction algorithms strongly affect CT texture analysis.
Answer 2:
We slightly disagree with the reviewer on the strong influence of the reconstruction algorithm on texture parameters. Previous studies (Kolossváry et al., 2019) have demonstrated that differences in CT reconstruction algorithms have limited effect on texture parameters in comparison to other texture analysis parameters such as binning (please see page 16).
During unsupervised analysis with hierarchical and k-means clustering, there was no difference in the distribution of the segments scanned and reconstructed with the different instruments (please see page 16).
Moreover, both machine learning models achieved similarly good prediction accuracies when tested separately on livers scanned with either a 16-slice or a 64-slice scanner. The ROC AUC of the RFC model was 0.822, 95% CI: 0.601-1.00 in the 16-slice and 0.864, 95% CI 0.776-0.953 in the 64-slice group using repeated 5-fold cross-validation. The AUC of the SVM model was 0.868, 95% CI 0.749-0.987 in the 16-slice and 0.781, 95% CI: 0.76-0.802 in the 64-slice group. This information is now included in the manuscript (please see page 13).
Also, previous reports, which evaluated texture parameters in different stages liver fibrosis achieved similar classification accuracy with multiple scanners (Pickhardt et al., 2019). Therefore, we can conclude that CT scans performed with either of the two instruments discussed in our study can be used with similar success for prediction of high-grade fibrosis using texture analysis (please see page 16).
Kolossváry, M., Szilveszter, B., Karády, J., Drobni, Z.D., Merkely, B., Maurovich-Horvat, P., 2019. Effect of image reconstruction algorithms on volumetric and radiomic parameters of coronary plaques. Journal of Cardiovascular Computed Tomography 13, 325–330. https://doi.org/10.1016/j.jcct.2018.11.004

Pickhardt, P.J., Graffy, P.M., Said, A., Jones, D., Welsh, B., Zea, R., Lubner, M.G., 2019. Multiparametric CT for Noninvasive Staging of Hepatitis C Virus-Related Liver Fibrosis: Correlation With the Histopathologic Fibrosis Score. AJR Am J Roentgenol 212, 547–553. https://doi.org/10.2214/AJR.18.20284

Materials and Methods

1. Please clarify the duration between CT scan and US elastography study. If patients with long duration exist, I think it is not proper to include the cases in the study

Answer 1:
We thank the reviewer for pointing out this important technical detail. The shear-wave elastography measurement was performed within 6 months of the CT scan. We think it is an acceptable time frame, since patients with advanced fibrosis are followed-up in six-month intervals, thus fibrosis status is not expected to change significantly in shorter periods. This information is now included in the revised form of the manuscript (please, see page 5).

2. The fact that two patients were excluded from the study due to lack of contrast-enhanced CT should be presented in the study population section.

Answer 2:
We have corrected the study population section according to the reviewer's request (please, see page 5).

3. For the CT scan, the contrast agent's injection rate has a wide variety (2-3.5ml/sec). Is this due to a fixed injection duration? Please clarify in detail how the contrast agent was injected.

Answer 3:
The volume of contrast was calculated for the patients’ lean body weight (500 mg of iodine/kg). The injection rate was adjusted to achieve a fixed injection time of 30 seconds. The bolus tracking method was used for timing the scan, where an ROI was placed in the lumen of the descending aorta, above the diaphragm. The portal venous phase scan was initiated 60 seconds after the aortic enhancement in the ROI exceeded the 150 HU threshold. The corrected description is now included in the manuscript (please see page 7).

4. line 141 Which level of the aorta? Please clarify.

Answer 4:
The ROI used for bolus tracking during contrast injection was placed into the lumen of the descending aorta, above the diaphragm. This detail is now included in the revised manuscript (please, see page 7).

5. It seems that a liver is divided into nine segments if we judge from Figure 1. Although in the result section, 354 anatomic liver segments were extracted from 30 patients. This discrepancy should be explained.

Answer 5A:
We thank the reviewer for drawing attention to this missing information in the materials and method section. In general, 12 liver segments including nine anatomic liver segments, the right and left lobes as well as the whole liver, were manually annotated in 30 patients with portal venous phase scan. One of the patients had prior resection of the right posterior-lateral segment (S6), we also detected circumscribed lesions such as hepatic cysts in the S3 segment of one and in the S4A and S4B segments of two patients. Therefore, altogether six liver segments were omitted from the analysis and the final dataset consisted of 354 liver segments. This information is now included in the revised manuscript (please see page 8).

Also, it seems that the horizontal line is separating the upper and lower zone of the liver, but how? This does not match with usual anatomical segmentation.

Answer 5B:
The liver segmentation was performed manually on axial slices. The slice with the greatest cross-section at the bifurcation of the portal vein was used for the separation of upper and lower segments in each lobe, which provides a good approximation of the anatomical liver segments. This information is now provided in the manuscript (Please, see page 7). We agree with the reviewer that the 3D image on panel A of figure 1 may not be the most accurate representation of the surface view of the liver segments. Therefore, we have changed the image in this panel to show more proper segment boundaries (please see the revised Figure 1).
6. How the patients were split to training and test sets should be presented. Also, the distribution of the fibrosis stage in each set should be presented.

Answer 6:
The liver segments were randomly divided into equal size training and test set including 177 samples each for machine learning analysis. The proportion of cirrhotic and non-cirrhotic liver segments was similar in the training (non-cirrhotic 48, 27%, cirrhotic 129,73%) and test (non-cirrhotic: 59, 33%, cirrhotic 118, 67%) groups. The revised manuscript now contains this information (please, see page 12). The number of liver segments also has been corrected on page 12 and on Figure 2 (please see the revised Figure 2).

#Reviewer 2:
This paper shows the role of CT texture analysis to differentiate highgrade from low-grade fibrosis irrespective of the imaging platform.
The theme is novel; In literature, there are no studies about this topic.
The manuscript is nicely written, and the content is simple and easy understanding.

Answer 1:
We agree with reviewer 2 that CT texture analysis is a useful tool to predict high-grade fibrosis irrespective of the scanning platform, and thank him/her for the favorable comments.