Reviewer’s report

Title: Blood Oxygen Level Dependent Magnetic Resonance Imaging for Detecting Pathological Patterns in Lupus Nephritis Patients: A Preliminary Study Using a Decision Tree Model

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Reviewer: Steven Sourbron

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Summary

The purpose of this study is to investigate if BOLD MRI parameters (R2*) are able to predict histological classification and subclassification of lupus nephritis. Paired MRI-histology data were collected in 12 patients across pathological classes III and IV. MRI data consisted of 10 R2* histogram metrics for regions covering the kidney. Paired data were used to train three different statistical models in predicting the pathological class and subclass on the basis of the R2* values. The best model (decision tree) achieves and AUC ROC of 0.765 (sensitivity 0.718, specificity 0.639). A more refined analysis based on probabilities of prediction and subdivisions of the images predicts histological class correctly in all cases, and predicts subclass correctly in all but one case.

General comment

The paper is very interesting and the results are strong - but for this reason I believe they also deserve closer scrutiny and better clarification of key ingredients of the methodology and study setup.

Specific comments

1. It is not clarified in the paper which data were used as a basis to develop and train the MR image processing methods and statistical methods (training data), and which data are used to validate the methods (test data). There is some mention of cross validation (p7,63), but as far as I understand from the explanation that is only applied after fixing the methods, so the role of it is not clear to me. If the training data and the test data are the same, this is a serious limitation that must be acknowledged and properly taken into account in the interpretation. MRI images contain vast quantities of information and in principle almost unlimited numbers can be extracted from the data - increasing the probability that a good classification can be achieved through pure chance alone. This is all the more true because the number of
cases is small and $R2^*$ is not very precise. Extrapolating from previous studies a 10-20\% coefficient of variation for median $R2^*$ is not unreasonable, presumably significantly more for less precise parameters (skewness etc) and when physiological fluctuations are taken into account. This means that the probability of finding a good classification in N=12 training data due to chance alone may actually be quite high, but as far as I can see these effects are not accounted for in the analysis.

2. There are key elements of the MR image processing aspects that are not sufficiently clearly explained, even though they are quite crucial to the conclusions. I am referring specifically to the aspects mentioned in p6, line 23 onwards referring to the subdivision of each ROI in 100 randomly selected groups of 100 consecutive voxels. It is not clear at all to me how this is done exactly, what data are extracted and how they are used to generate probabilities and classifications. The authors return to this part of the methods in the discussion section (p10,51 and onwards) explaining that this is a new methodology developed for this project with some more details on the approach - though it remains unclear to me what they have done exactly. They also attempt a justification in terms of heterogeneity but the explanation is confused and unfortunately doesn't help me to gain additional insight in what this does or why.

3. What this study is also lacking is a clear hypotheses to justify why there would be a role for BOLD in LN. $R2^*$ is sensitive to blood oxygenation, but is there a reason why one would expect this to help in the subclassification of LN? What exactly is the role of blood oxygenation in LN pathogenesis? What changes would one expect and can these be related to differences seen on the histology? The only motivation the authors are giving for this study is that it hasn't been done (p4, 48). Another issue is that the authors discuss BOLD only in terms of oxygenation but the effect of microstructural changes in $R2^*$ are equally important and must be taken into account in the interpretation.

4. P5, MRI techniques: there are important details missing in the technical specification of the imaging methods. For instance is this done in free-breathing? Breath hold? Triggered? 2D or 3D sequence? What slice orientation? Is parallel imaging used etc.. Full details of the key sequences need to be provided.

5. P6, Algorithm models: more details about the models need to be provided and references need to be given.

6. P7, 25. Why only 4 patients?

7. P7, 51. How were the user-specified levels chosen? This may relate to point 1)

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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