**Title:** Liver Shape Analysis using Statistical Parametric Maps at Population Scale

**Version:** 6 **Date:** 23 Oct 2023

**Reviewer's report:**

This authors provided responsive edits to the manuscript to address my statistical concerns. While the authors refused to recognize or discuss the potential impact of segmentation and registrations errors on their approach, this reviewer believes that this point should not be a barrier towards publication of the authors' undoubtedly impressive work. However, this reviewer would caution the authors going forward that although the S2S distances may be relevant at the population scale where the confidence interval around an average trend may be narrow enough to detect statistical significance, the prediction interval for an individual patient, which statistically does not benefit from the same large cohort size, may be worrisome due to high sample variances arising from error sources such as the aforementioned uncertainties in segmentation and registration. As this work continues to develop, it will remain to be seen how well the S2S distances as potential biomarkers will perform in reproducibility and reliability studies that eventually will be necessary for the proposed ideas to be clinically recognized and adopted.