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# Is Room Temperature Susceptometer really an accurate method to assess hepatocellular iron?

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Dear Editor,

We read with interest the study by Mueller et al. describing the use of room temperature susceptometer (RTS) to assess hepatic iron content (HIC) (1). This is an interesting clinical application of the methods described by Arvin et al. (2, 3). This topic is relevant as there is still a need for cost-effective and efficient iron quantification method in liver disease.

However we think that several points could benefit from clarification and that more cautious conclusion should be drawn from these results. Overall as a diagnosis accuracy study it would have been beneficial to follow the STARD statement to avoid some pitfalls (4).

- Although the main purpose of this study is to describe diagnosis accuracy of RTS, only the global screening population is described. However most of the results and discussion are based on the 35 patients who had liver biopsy. Based on information we can infer from Figure 4 it seems that only 9(27%), 5(15%) and 1(3%) patients had LIC AAS higher than 2 mg/g (which is the normal value), 5 mg/g and 7 mg/g respectively. This yield a very low prevalence of significant iron overload that can have a direct impact on the accuracy value of tests (5). Moreover these potentials patients with iron overload are not described.
- As liver biopsy is an invasive test and as emphasized by the authors is prone to sampling errors, Magnetic Resonance Imaging (MRI) could have been considered as a readily available surrogate gold standard to evaluate iron overload, either by T2\* calculation or liver to muscle ratio. However in this study that correlation was done only in a very limited number of patients.
- More specifically regarding patients with HFE hemochromatosis, Figure 4 shows similar RTS value for two patients that have striking different HIC. This may raise concerns about the reproducibility of RTS in patients with significant iron overload, and further emphasize the issue of low iron overload prevalence in the study population. Moreover this should be discussed when the authors suggest the use of RTS to follow bloodletting treatment in these patients.
- To further assess the accuracy of RTS compared to atomic absorption spectroscopy (AAS) the authors use Bland-Altman plot. However, only truncated results are shown for HIC higher than 2 or 4 mg/g. It would be informative to the reader to show the actual overall bias (mean of difference,  $d$ ), precision (SD), and limits of agreement ( $d \pm 1.96SD$ ) as usually reported using this method. (6)
- Although their results show that RTS have a good correlation with a well-acknowledged gold standard for HIC (liver biopsy with AAS), the authors assess diagnosis accuracy in regard to the semi quantitative evaluation of hepatocytes iron content (which has a lower correlation with RTS according to their own results). Assessing accuracy against a quantitative value would facilitate comparison with other studies, especially with MRI for which several studies described larger population of patients with gold standard liver iron quantification and with significant prevalence of iron overload. (5)

- The authors compare the accuracy of different tests for the diagnosis of hepatocellular iron overload  $\geq 2$ . It would have been interesting to compare the overall AUC of each test with an appropriate statistical method (7) rather than comparing the sensitivity, specificity and predictive values, as they are significantly influenced by the selected cut-off. Given the power of the study it is surprising that transferrin saturation AUC (0.85, CI not shown in the manuscript) is significantly lower than that of RTS (0.89, CI:0.74-0.95). Moreover it should be noted that the 1000 ng/ml ferritin cut-off was designed to rule out significant liver fibrosis in HFE homozygous patients, but not to assess iron overload. In this setting serum ferritin may encompass more than HIC (8)
- Most of patients in the screening study had alcoholic liver disease. In such population steatosis prevalence is high which may, as emphasized by the authors, induce a bias for hepatic iron quantification.

Overall we think RTS is an interesting method that could help clinicians to screen for iron overload, however more thorough assessment is required for comparison to other non invasive methods before its use and development could be promoted.

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