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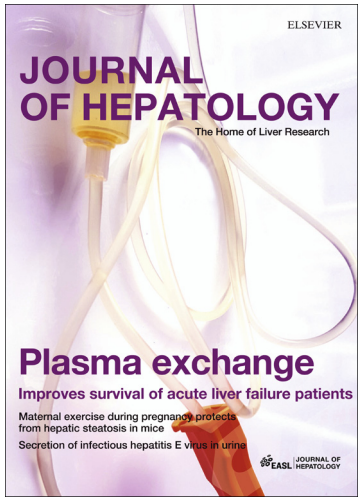

Multiparametric magnetic resonance imaging to predict clinical outcomes in patients with chronic liver disease: a cautionary note on a promising technique

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Rajeshwar Mookerjee – none to declare
Stuart Taylor – none to declare

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Manil Chouhan - prepared the manuscript, collated contributions from the other authors
Gareth Ambler – provided statistical advice, edited the manuscript
Rajeshwar Mookerjee – provided hepatological advice, edited the manuscript
Stuart Taylor – provided radiological advice, edited the manuscript

Multiparametric magnetic resonance imaging to predict clinical outcomes in patients with chronic liver disease: a cautionary note on a promising technique

To the Editor:

We have read the article by Pavlides et al.[1] with great interest. The potential of quantitative MR methods to predict clinical outcomes in patients with chronic liver disease is an important area of research and T1 mapping is undoubtedly a promising technique[2, 3]. The findings of Pavlides et al are therefore of potential importance.

We are however concerned that the study sample size and event rate are too small to draw definitive conclusions and so must be more cautious before we can assume clinical utility of T1 mapping for prognostication. Using a single-slice multimethod MR protocol (T1 mapping 'corrected' with T2* mapping data and MR spectroscopy), the authors monitored outcomes in just over 100 patients on average 27 months following an initial MRI scan. Their survival analysis is however based on adverse events in just 10 subjects (a number that reduces to 6 once patients with index decompensation at the initial MRI study are excluded). Comparatively, this sample size and event rate are much lower than comparable outcome studies for competitive biomarkers (e.g. FibroScan: n=2052, 87 adverse events[4]; enhanced liver fibrosis test: n=457, 61 adverse events[5]).

The authors propose a so-called 'Liver Inflammation Fibrosis' (LIF) score (a metric based on "corrected" T1 (cT1) which is unreferenced) and report a negative predictive value of 100% for adverse events using a cut-off of <2 (confidence interval 94-100%). However the positive predictive value for adverse events using this LIF score cut off is just 18% (confidence interval 9-30%). Thus only 1 out of 5 patients with an LIF>2 are likely to experience an adverse event. We agree that a LIF score <2 may be useful as a screening tool to identify those less likely to experience future complications, but as a tool to predict adverse clinical outcomes the data presented suggests LIF is actually relatively weak. Indeed, using the study data, the positive predictive value of an Ishak score of 5-6 is slightly better, but even then just 29% (9 events in 31 patients). This, taken together with the existing literature, highlights the intrinsic limitations of fibrosis scores in predicting clinical outcomes. There is for example, a significant representation of steatohepatitis in the 10 patients with liver events, for whom non-invasive scores such as the CLIF-C AD score have good predictive utility (AUROC>0.75)[6]. Comparisons with more established surrogate endpoints for disease progression such as hepatic venous pressure gradient would also offer more robust LIF score validation[7].

The survival analysis, whilst interesting, is also unfortunately compromised by the small sample size. Given the small number of adverse events (*n*=10), application of a Bonferroni correction to multiple post-hoc inter-group comparisons would likely render most of the 'strong tends towards significance' for survival according to LIF groups as definitively non-significant.

T1 mapping is a well-established technique, and multiple methods have been described in the literature, including the widely used shortened modified look-locker inversion recovery (ShMOLLI) technique[8]. cT1 was applied in 54% of the patient cohort (presumably the remaining 46% underwent uncorrected T1 mapping, although this is not clearly stated). The authors speculate that 'the enhanced ability of [their] technique to differentiate between histological stages may be due to the particular…T1 mapping technique we apply' (referring to the use of cT1). In fact, this conclusion could only be reached by comparing clinical outcome data using both cT1 and ShMOLLI methods.

The authors also state that cT1 correct standard T1 measurements by 'removing the confounding effect of liver iron'. However, whether physically the correction employed here is capable of fully correcting for the presence of additional iron, especially when only a single slice is considered, should be examined more closely. In fact, omitting liver iron correction actually improved the LIF hazard ratio (using the Cox regression model) for predicting adverse events. It is therefore unclear whether correction for liver iron is beneficial or otherwise, and again this needs formal investigation. Low grade siderosis can occur in chronic liver disease (in the absence of an iron

deposition disorder) and the effect of this on hepatic parenchymal T1 remains to our knowledge little explored. Data demonstrating the value of cT1 over other T1 mapping techniques in patients with non-iron deposition disorder chronic liver disease would be welcome in this regard.

Parenchymal T1 measurements reflect the complex underlying tissue composition and are thus influenced by many factors beyond extracellular water and iron, for example fat[9] and proteinaceous components (including extracellular matrix). We need more studies that comprehensively explore the quantitative relationship between liver tissue composition and T1 signal, before it can be concluded that cT1 measurements are a pure 'estimate of extracellular water'.

Finally, in the discussion, the authors rightly acknowledge the study is 'a small proof of principle study', but this perhaps should have been made clearer by the journal in the title and abstract. We agree with the authors that hepatic T1 mapping is definitely a promising approach for the quantification of liver pathology and that with high quality, well-powered supporting data could yield an important biomarker for all aetiologies of patients with chronic liver disease. Indeed multiparametric MRI as a whole, inclusive of other techniques that assess perfusion, biomechanical properties and whole liver (rather than voxel-based) fat quantification has transformative potential in liver diagnostics[10].

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