



Retraction notice to “Molecular forms of HMGB1 and keratin-18 as mechanistic biomarkers for mode of cell death and prognosis during clinical acetaminophen hepatotoxicity”

J Hepatol 56(2012)1070–1079

Daniel J. Antoine¹, Rosalind E. Jenkins¹, James W. Dear², Dominic P. Williams¹,
Mitchell R. McGill³, Matthew R. Sharpe⁴, Darren G. Craig⁵, Kenneth J. Simpson⁵,
Hartmut Jaeschke³, B. Kevin Park¹

¹MRC Centre for Drug Safety Science, Department of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, UK;

²University/BHF Centre for Cardiovascular Science, Edinburgh University & NPIS Edinburgh, Scottish Poisons Information Bureau, Edinburgh, UK; ³Department of Pharmacology, Toxicology & Therapeutics, University of Kansas Medical Center, Kansas City, KS 66160, USA;

⁴Department of Pulmonary and Critical Care Medicine, University of Kansas Medical Center, Kansas City, KS 66160, USA; ⁵Scottish Liver Transplantation Unit, Royal Infirmary of Edinburgh, Edinburgh, UK

This article has been retracted: please see Elsevier Policy on Article Withdrawal (<http://www.elsevier.com/locate/withdrawalpolicy>).

This article has been retracted at the request of the Editor-in-Chief and Authors.

Concerns were raised by one of the Co-Authors and the University of Liverpool regarding the reliability and replicability of the research undertaken into the HMGB1 isoforms, including their potential use to inform mechanisms, diagnosis and prognosis of various disease states.

After numerous subsequent analyses, the assays and data for cytokeratin 18 and total HMGB1 have proven to be reproducible, either from direct reanalyses or from parallel studies.

The Authors were able to re-analyse a subset of 35 original clinical samples for total HMGB1 (using the same commercial ELISA assay as that used in the paper) and found a strong correlation with the original data. We have re-analysed clinical samples from a separate paracetamol overdose patient cohort for these markers (and reported in a separate paper, *Risk stratification after paracetamol overdose using mechanistic biomarkers: results from two prospective cohort studies*; J.W. Dear, J.I. Clarke, B. Francis, L. Allen, J. Wraight, J. Shen, *et al.*; *Lancet Gastroenterol Hepatol.* 2018 Feb; 3(2):104-113 PMID: [29146439](https://pubmed.ncbi.nlm.nih.gov/29146439/)). The analyses again showed a strong correlation. Furthermore, the repeat keratin 18 analyses from this second cohort, together with separate work by one of the paper's co-authors, Dr Ken Simpson,

on a study of acute liver failure patients following paracetamol overdose (*Circulating apoptotic and necrotic cell death markers in patients with acute liver injury*; D.G.N. Craig, P. Lee, E.A. Pryde, G.S. Masterton, P.C. Hayes, K.J. Simpson; *Liver International*, 31(8) (2011) pp. 1127-1136 PMID: [21745283](https://pubmed.ncbi.nlm.nih.gov/21745283/)) replicated the findings for both forms of this biomarker.

The Authors are therefore confident that the bioanalytical readouts and clinical implications from the original total HMGB1, caspase-cleaved keratin 18 and total keratin 18 data are correct.

However, in respect to acetylated HMGB1, after various approaches and reanalyses the methodology cannot be reproduced as described in the paper and therefore the authors and the University of Liverpool have been unable to verify whether the data for this analyte are correct and reproducible.

The method for acetylated HMGB1 quantification has two main components: isolation of the HMGB1 analyte from clinical samples using immunoprecipitation and subsequent protein digestion and mass spectrometric analysis of the HMGB1 peptides. The Authors are confident that the mass spectrometry protocol is robust but they have been unable to recapitulate the immunoprecipitation and digestion. They are working on new methods, with collaborators, to identify all HMGB1 isoforms.

As a consequence of the above, and the central importance of the acetylated HMGB1 data to the scientific trustworthiness, the decision has been made to retract the paper.

DOI of original article: <https://doi.org/10.1016/j.jhep.2011.12.019>.
<https://doi.org/10.1016/j.jhep.2020.08.022>



ELSEVIER