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**Faecal proteomics links neutrophil degranulation with mortality in patients with alcohol-associated hepatitis**

Kreimeyer H, Gonzalez C, Fondevila M, *et al.* Faecal proteomics links neutrophil degranulation with mortality in patients with alcohol-associated hepatitis. *Gut* 2025; 74: 103-115. doi: 10.1136/gutjnl-2024-332730

The severe form of alcohol-associated hepatitis (AH) has poor short-term mortality and identification strategies on who to receive therapy remain limited. Kreimeyer *et al.,* report an investigation of faecal proteome signatures with tandem mass tag mass spectrometry in AH (n=80), alcohol use disorder (AUD, n=20) and healthy controls (HC, n=19) from a multicentre cohort.

Following principal component analysis using PERMANOVA (permutational multivariate analysis of variance) they showed three distinct proteome subgroups, with separation of HC from other disease groups, but no difference between AH and AUD. Specific protein quantitative differences revealed that 261 and 149 proteins showed differences between all three groups, and AUD vs. AH, respectively. Of these 101 were expressed differently in AH compared to AUD or HC. Kreimeyer *et al.,* then focused their investigation on 12 proteins which had progressive interval change between HC, AUD and AH. These proteins clustered into three groups: neutrophil function (MPO (myeloperoxidase), CTSG (cathepsin G), HBB (Haemoglobin B), LAMP1 (Lysosome-associated membrane glycoprotein 1), ORM2 (orsomucoid 2), muscle function (MYL11 (myosin light chain 11), MYL1 (myosin light chain 1), nebulin, ATP2A1 (sarcoplasmic/endoplasmic reticulum calcium ATPase 1)) and others (HBD (haemoglobin delta), IGLV7–47 (immunoglobulin light chain 7–47)). Gene ontology and reactome analysis showed similar pathways affected in AH.

With correlation analysis of protein quantity and clinical parameters related to liver disease, they further selected MPO and nebulin for further analysis. They showed MPO cutoff levels derived from maximally ranked statistics differentiated 60-day mortality in AH and replicated these findings in an independent validation cohort.

In summary, Kreimeyer *et al.,* characterised the faecal proteome signature and showed MPO levels may stratify mortality in AH. Further longitudinal and functional studies are required to replicate and determine their clinical usability and mechanistic role.