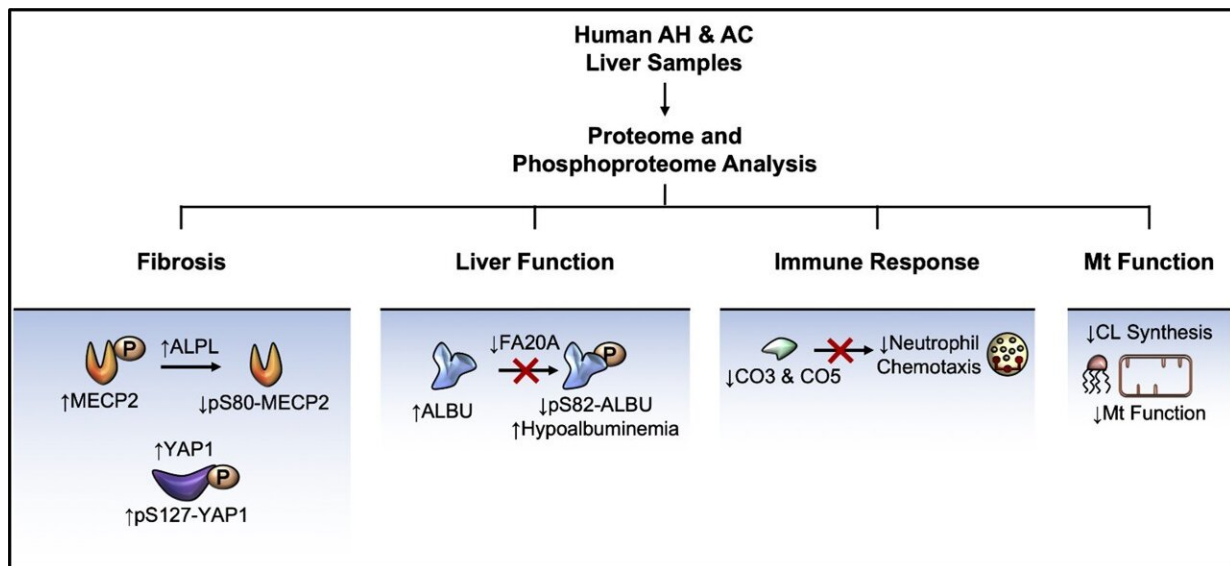


Factors that contribute to alcoholic liver disease

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Overview of hepatic proteomic and phosphoproteomic signatures identified in alcohol-associated hepatitis (AH) and alcohol-associated cirrhosis (AC). Hepatic neutrophils and chemoattractants are reduced in later stages of AH. Cardiolipin synthesis is compromised in AH and AC. These are newly identified metabolic defects and are likely to lead to the development/progression of AH/AC. Credit: *American Journal of Pathology*

The most common form of liver disease, alcohol-associated liver disease (ALD), contributes to half a million cirrhosis deaths worldwide annually. Odds of survival are very low and treatment options are limited. Two manifestations of ALD have a particularly poor prognosis: alcohol-

associated hepatitis (AH) and alcohol-associated cirrhosis (AC). A team of researchers investigating the underlying causes of AH and AC observed significant alterations in multiple proteins involved in various biological processes in both diseases that may serve as biomarkers or treatment targets. Their research and dataset appear in the *American Journal of Pathology*.

"Many AC and AH patients are unaware of the severity of their condition, and there are very few medical treatment options available," explained lead investigators Irina A. Kirpich, Ph.D., MPH, University of Louisville, Louisville, KY, and Jon Jacobs, Ph.D., Pacific Northwest National Laboratory, Richland, WA, U.S. "This problem has intensified over time, and the COVID-19 epidemic has exacerbated alcohol-related hospitalizations. There is a real necessity for the identification and development of biomarkers and treatments."

Dr. Kirpich, Dr. Jacobs, and their colleagues conducted the first tandem proteomic and phosphoproteomic analysis on [liver](#) tissues from AC and AH patients. Proteomic analysis determines the proteins that are altered under disease conditions. Phosphoproteomic analysis determines the phosphorylation status of these proteins, which plays a role in many cell functions including inflammation, metabolism, proliferation, and cell death. They analyzed liver samples from two independent groups of AH patients and one subset of AC patients to identify novel [protein](#) and phosphoprotein signatures of AC and AH as well as AH severity. AH patients were divided into four groups based on their Model for End-Stage Liver Disease (MELD) score, which ranks the severity of a patient's [disease](#), with higher scores for more critical illness.

This research identified metabolic defects that are likely to lead to the development and progression of AH and AC, including impaired liver protein secretion, impaired neutrophil function, and impaired liver regeneration. They found that [protein synthesis](#), a critical function

commonly compromised in chronic [liver disease](#), was altered in AH and AC. They identified elevated albumin protein expression in the liver, but with reduced phosphorylation, which may prevent the release of albumin to the blood. This could contribute to severe hypoalbuminemia (low levels of albumin in blood) seen in these patients, which is a hallmark of liver failure. They also identified multiple pro-fibrotic transcription factors that were associated with AH severity.

Another finding was that hepatic neutrophil markers and chemoattractants follow a bell-shaped curve according to AH severity—they were elevated in patients with MELD scores between 17 and 25 but were decreased in patients with MELD scores greater than 25. This may have implications for when to administer immunomodulatory drugs such as prednisolone. Finally, synthesis of hepatic cardiolipin was compromised in AC and AH, which could impact mitochondrial function and liver repair and regeneration.

MECP2 phosphorylation was reduced in AH and YAP1 expression was increased in AH despite elevation of pS127-YAP1, which is a signal for YAP1 degradation. ALBU expression was increased in AH and AC, but phosphorylation was reduced possibly contributing to hypoalbuminemia.

"This one-of-a-kind study and its novel proteomic dataset will provide a roadmap for the development of novel biomarkers and therapies for AH and AC and," said Dr. Kirpich and Dr. Jacobs. "We are optimistic that findings from this study will be utilized by many investigators in the field for years to come and could therefore help finetune current treatment strategies to improve patient outcomes and open the door to new paradigms and ideas to improve patient care."

More information: Josiah Hardesty et al, Hepatic Protein and Phosphoprotein Signatures of Alcohol-Associated Cirrhosis and Hepatitis, *The American Journal of Pathology* (2022). [DOI:](#)

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