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Systemic Activin Is Elevated in Patients With Severe Alcoholic Hepatitis

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Severe alcoholic hepatitis (sAH) presents as jaundice with liver failure in patients with chronic alcohol misuse.[1] Prognosis is dire with ~30–40% of patient deaths occurring within 6 months after diagnosis.[2] Treatment options are limited to glucocorticoid therapy, although the evidence regarding a mortality benefit is inconclusive.[3] Activins are cytokines and members of the transforming growth factor-β superfamily with key functions in inflammation,[4] liver fibrosis and regeneration,[5] and several other homeostatic functions. Activin has 2 known endogenous inhibitors: follistatin, a specific ligand trap, and inhibin, which competitively binds to the Activin type 2 receptor (ActRII).[6]

Several studies and models have identified activin's anti-inflammatory effect on innate immune cells, specifically neutrophils, and its regulatory effect on the adaptive response.[4] There is also recent evidence for activin as supporting sepsis in patients with COVID-19.[7]

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Ethical Statement:

The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:

All data and materials are provided in the manuscript.

Supplementary Materials

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Furthermore, activin has been shown to have a direct effect on liver function with high levels of activin stimulating hepatocyte apoptosis and inhibiting liver regeneration in models of injury.[5] Neutrophil infiltration of the liver parenchyma and impaired liver regeneration are central aspects of sAH.[1] Because neutrophil infiltration of the liver parenchyma and impaired liver regeneration are central aspects of sAH[1] and given the well-described role of activin in both the activation of neutrophils and liver homeostasis, we hypothesized that activin levels would be increased in sAH. Additionally, we predicted that higher activin levels would associate with worse prognosis in sAH owing to activin's role in driving inflammation and inhibiting liver regeneration. Here, we present the first study of systemic activin A and follistatin levels in a cohort of patients with sAH.

We measured activin A and follistatin serum levels and calculated the activin A-to-follistatin (A/F) ratio in 83 patients with sAH from San Diego, CA, USA, recruited to the STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH, Project #160763X) trial cohort. Patients were grouped by 28-day mortality (died: n = 43), matched for baseline Model For End-stage Liver Disease (MELD) score, and split between those treated with (n = 39) and without (n = 44) prednisolone. Control groups comprised healthy volunteers (n = 13) and patients with alcohol use disorder (AUD) without known liver disease (n = 9). Circulating levels of platelets, bilirubin, liver enzymes (alanine aminotransferase, aspartate transaminase, and alkaline phosphatase), albumin, creatinine, and international normalized ratio for blood clotting were measured to confirm disease state and severity across patients. Inclusion criteria included age (≥18 years), a clinical diagnosis of alcoholic hepatitis, an average alcohol consumption of >80 g per day for men and >60 g per day for women, a serum bilirubin level >4.7 mg per deciliter (80 mmol per liter), and a discriminant function of ≥32. Key exclusion criteria were jaundice for more than 3 months, cessation of alcohol consumption for more than 2 months before randomization, the presence of other causes of liver disease, a serum aspartate aminotransferase level >500 IU per liter or serum alanine transaminase level >300 IU per liter, and previous entry into the study within the preceding 6 months. Cohort characteristics are included in Table A1.

When comparing patients with AUD with controls, we found no statistical difference in median serum activin A (3.25 ng/mL vs 2.42 ng/mL, $P = .108$, Figure A) but detected slightly elevated follistatin (1.725 ng/mL vs 1.175 ng/mL, $P = .017$, Figure B). Owing to the inhibitory nature of follistatin, it is essential to calculate the A/F ratio to determine net signaling. The A/F ratio was not statistically different between these 2 groups (0.220 vs 0.242, $P = .578$, Figure C). When comparing patients with sAH with controls, we found significantly increased levels of activin A (sAH 4.38 ng/mL vs AUD 0.325 ng/mL vs control 0.242 ng/mL, $P < .001$, Figure A), follistatin (10.76 ng/mL vs 1.725 ng/mL vs 1.175 ng/mL, $P < .001$, Figure B), and the A/F ratio (0.39 vs 0.22 vs 0.21, $P < .005$, Figure C), indicating dysregulation of activin signaling in response to sAH.

When comparing the activin A levels in our sAH cohort with published activin A levels in other diseases, our data indicate that activin A levels in sAH significantly exceed serum levels in a multitude of liver conditions including stage IV primary biliary cirrhosis,[8] chronic hepatitis C and hepatitis B,[9] and acute liver failure of viral or toxic etiology.[10] Furthermore, the upregulation of both activin A and follistatin in the patients with sAH suggests severe

dysregulation of the system with a net increase in signaling based on the A/F ratio. To determine whether serum activin A levels predicted mortality independently of disease severity, we matched cohorts of survivors and nonsurvivors using the baseline MELD score. We hypothesize that in a less homogenous cohort with differing MELD scores, activin, follistatin, and the A/F ratio might have a predictive value with regards to mortality. Additionally, given activin's proinflammatory effect on neutrophils, treatment with an immunosuppressive agent may mask a predictive effect on activin serum levels. Following repetitive and chronic ethanol insults to the liver, the activin A signaling cycle is disturbed and a neutrophil-driven inflammatory response begins in the liver. This decompensation presumably leads to a disturbance in the otherwise tightly controlled activin signaling pathways where activin A, likely secreted largely by invading neutrophils, leads to both repressed hepatocyte DNA replication and inhibited liver regeneration, as well as ongoing neutrophil activation. This may also lead to the vicious cycle of hepatic inflammation and repressed liver regeneration seen in sAH and mirrored in the dire prognosis of these patients.

Current animal models lack key aspects of acute alcoholic hepatitis in humans, rendering in vivo work limited. Here, we present novel data establishing a basis for future studies to improve patient outcomes in sAH. Although this study is limited by size, several previously published studies have identified control levels near what is reported here and that several other diseases of the liver do not induce circulating levels of activin A at the level observed in sAH.[8–10] Activin is an emerging target for pharmacological inhibition, and delineation of potential subgroups most likely to respond to antiactivin therapy would be crucial to inform future clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper:

A/F ratio	activin-to-follistatin ratio
AUD	alcohol use disorder
sAH	severe alcoholic hepatitis

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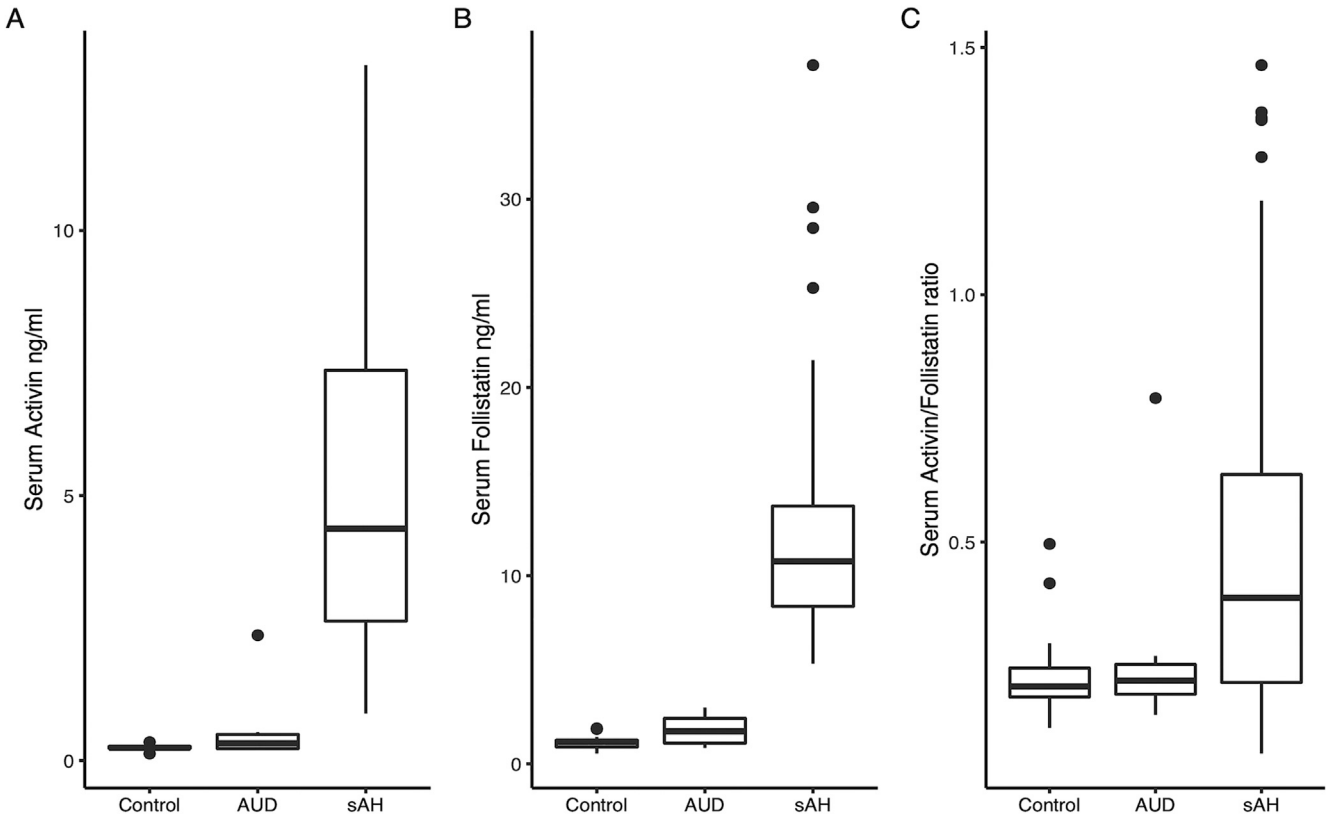

Figure.

Circulating levels of activin A (A), follistatin (B), and the activin-to-follistatin ratio (C) in control, alcohol use disorder (AUD), and severe alcoholic hepatitis (sAH).