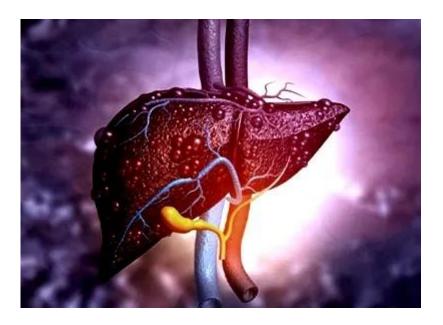


As liver disease progresses and complications, such as ascites, hepatic encephalopathy, variceal bleeding, or acute-on-chronic liver failure (ACLF) develop, patients with compensated advanced chronic liver disease (ACLD) progress to decompensated ACLD. Insulin-like growth factor 1 (IGF-1) is mainly produced in hepatocytes, and its secretion is influenced by somatotropin (STT), insulin, and nutritional status. IGF-1 levels have been observed to correlate with liver functional capacity, which has been considered a marker of hepatocellular function in advanced chronic liver disease. In this study, the Austrian authors investigated the STT-IGF-1 axis at different clinical stages of liver cirrhosis and parameters potentially related to plasma levels of STT and IGF-1.

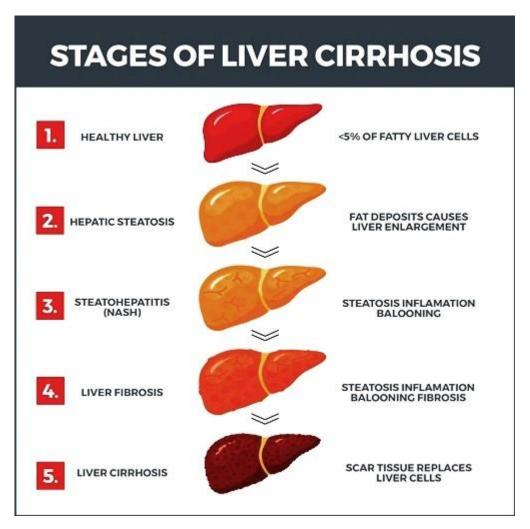


### About the study

This prospective study included consecutive patients with suspected ACLD, who underwent the diagnostic gold-standard hepatic venous pressure gradient (HVPG) measurement. The exclusion criteria were as follows: active malignancy including hepatocellular carcinoma outside of Milan criteria, liver transplantation, cholestatic liver disease, transjugular intrahepatic portosystemic shunt, acute liver injury, vascular liver disease including portal vein thrombosis, congestive heart disease, and insufficient clinical/laboratory data. The included patients were stratified according to the clinical stages of ACLD severity. The child-Turcotte-Pugh (CTP) score and the United Network for Organ Sharing (UNOS) Model



for End-Stage Liver Disease (MELD) score of 2016 were used as parameters of hepatic dysfunction.



Both the HVPG assessment and blood analysis were performed under fasting conditions. Blood was taken immediately after HVPG and resting in the supine position for at least 30 min. Serum levels of IGF-1 and STT were analyzed by chemiluminescent immunoassay (CLIA).

In patients with compensated ACLD, decompensation events were the occurrence of moderate-to-large ascites, clinically overt hepatic encephalopathy, or variceal bleeding. In decompensated ACLD, further decompensation was defined by either the occurrence of a second type of hepatic decompensation or the worsening of the existing decompensation. For patients decompensated with ascites, worsening was defined as the development of



spontaneous bacterial peritonitis or refractory ascites. For patients with a history of bleeding from esophageal varices, worsening was defined as a second variceal bleeding event.

During the follow-up, researchers evaluated the onset of defined events, including further decompensation, acute kidney injury, acute-on-chronic liver failure, and liver-related death.

#### Results

The study included 269 patients with probable ACLD or ACLD. A median age was 58.9 years, and most patients (69%) were men. The main etiologies of ACLD were alcoholrelated liver disease (47%), viral hepatitis (14%), and metabolic dysfunction-associated steatohepatitis (11%). 60% of patients had decompensated ACLD, 54% of them due to ascites.

## The analysis of somatotropin and insulin-like growth factor-1 plasma levels in patients with ACLD

The proportion of patients with low levels of IGF-1 gradually increased across different clinical stages of advanced chronic liver disease and was particularly high in those with decompensated liver cirrhosis. Patients with clinically significant portal hypertension also had significantly lower levels of IGF-1. Patients with low levels of IGF-1 were significantly younger than patients without low IGF-1 (51.8 years vs. 62.7 years). Interestingly, the proportion of patients with elevated somatotropin levels remained unchanged across different clinical stages of cirrhosis.

Patients with low IGF-1 had a higher prevalence of decompensated cirrhosis, further decompensation, and acute-on-chronic liver failure than patients without low IGF-1. They also had a higher prevalence of severe liver dysfunction, a higher hepatic venous pressure gradient, lower mean arterial pressure, higher IL-6 levels, higher scores on the Enhanced Liver Fibrosis (ELF) Test, and higher levels of fibrogenesis biomarkers: tissue inhibitor of metalloproteinase-1, amino-terminal type III procollagen peptide, and hyaluronic acid. They were more likely to undergo liver transplantation and were more likely to die from liverrelated causes. After adjustment for clinically relevant cofactors, the results showed that a low IGF-1 level was associated with a higher risk of further decompensation, acute-onchronic liver failure, and liver-related death. In contrast, multivariate analysis demonstrated



that the level of somatotropin was not associated with adverse outcomes.

There was no correlation between plasma levels of somatotropin and IGF-1, suggesting a dysregulated STT-IGF-1 axis in cirrhosis. However, there were moderate correlations between both STT and IGF-1 and ELF Test as a marker for liver fibrosis. IGF-1 was also correlated with fibrogenesis biomarkers, such as tissue inhibitor of metalloproteinase-1, amino-terminal type III procollagen peptide, and hyaluronic acid. Multivariate linear regression analysis demonstrated that IGF-1 (but not STT) was independently associated with the ELF Test, linking IGF-1 signaling to liver fibrosis development. This result is consistent with previous data showing that IGF-1 deficiency impacts liver fibrosis.

Both STT and IGF-1 were also correlated with liver dysfunction, portal hypertension, endothelial dysfunction, total bile acids, and systemic inflammation (IL-6). Interestingly, IGF-1 correlated with a parameter of hyperdynamic circulation (pro-brain-type natriuretic peptide). Multivariate linear regression analysis demonstrated that STT and IGF-1 were independently linked to UNOS MELD, parameters of hepatic dysfunction. Also, BMI, albumin, and age were independently linked to IGF-1, showing particularly low levels of IGF-1 in obese patients with liver cirrhosis. Previous data suggest that the Western-type diet contributes to the pathogenesis of nonalcoholic steatohepatitis, which rapidly becomes the leading cause of chronic liver disease.

https://discovermednews.com/the-western-type-diet-contributes-to-non-alcoholic-steatohepat itis/

### Follow-up and clinical outcomes

The median follow-up time was 604 days. Overall, 37% of patients (n = 100) experienced at least one further decompensation event during follow-up. 2.2% (n = 6) developed hepatocellular carcinoma, 8.5% (n = 23) had transjugular intrahepatic portosystemic shunt (TIPS) implantation, and 7.0% (n = 19) underwent liver transplantation. 52 patients (19%) died, and 34 of 52 patients died (65.4%) of liver-related causes.

IGF-1 had an excellent AUROC for predicting liver-related death after 6 months of follow-up. In addition, the cumulative incidence of liver-related death was approximately 4 times higher among patients with low IGF-1 at 1 year and 2 years of follow-up.



### **Conclusion**

This large prospective study demonstrated a significant decline in IGF-1 levels in progressive clinical stages of advanced chronic liver disease. Low plasma levels of IGF-1 correlated with parameters of liver dysfunction, fibrogenesis, and BMI. Lower levels of IGF-1 were an independent risk factor for further decompensation, acute-on-chronic liver failure, and liver-related mortality, highlighting the clinical significance of low IGF-1 in liver cirrhosis.

These results show that IGF-1 levels represent a valuable and clinically relevant prognostic biomarker in patients with advanced chronic liver disease. However, the authors emphasized that this study design could not establish a causative association between a decreased level of IGF-1 and adverse clinical outcomes. Therefore, it remains unclear whether a lower level of IGF-1 should only be seen as a prognostic biomarker or can serve as a therapeutic target.

Future studies should investigate whether adding IGF-1 to currently used risk stratification markers such as MELD or LSM may improve the prediction of liver-related events.

### Journal Reference

Hartl L, Schwarz M, Simbrunner B, et al. Insulin-like growth factor-1 in cirrhosis is linked to hepatic dysfunction and fibrogenesis and predicts liver-related mortality. Aliment Pharmacol Ther. 2025; 61:88-98. (Open Access) https://doi.org/10.1111/apt.18289