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**Gene score to quantify systemic inflammation in patients with acutely decompensated cirrhosis**

**Trebicka J, Aguilar F, Queiroz Farias A, et al. Gene score to quantify systemic inflammation in patients with acutely decompensated cirrhosis. Gut 2025; 74(8):1293-1307. doi: 10.1136/gutjnl-2024-333876.**

This study introduces and validates the CLIF-Systemic Inflammation Gene (CLIF-SIG) score, a novel transcriptomics-based biomarker for quantifying systemic inflammation (SI) in patients with acutely decompensated cirrhosis (ADC). Recognising the limitations of conventional biomarkers (e.g., CRP (C-reactive protein), WCC (white cell count), cytokines), Trebicka et al. analysed RNA-sequencing data from 700 hospitalised ADC patients across the PREDICT and ACLARA studies. A 28-gene signature reflecting immune cell-related expression changes was used to compute the CLIF-SIG score, stratifying patients by SI severity and prognosis.

The CLIF-SIG score significantly outperformed a composite of traditional biomarkers (CLIF-SBC) in differentiating patients with high-severity phenotypes (ACLF or early pre-ACLF) from those with lower severity. A threshold score of 0.386 (Youden Index) best predicted poor outcomes, with 80% of patients who developed ACLF during hospitalisation presenting above this cut-off. Importantly, the score’s predictive accuracy was consistent across liver disease aetiologies, demographics, and precipitating events.

Serial measurements revealed that SI in ADC progresses through distinct inflammatory phases, often beginning prior to hospitalisation. The score captured these dynamics and closely tracked 28- and 90-day mortality, independent of MELD-Na (Model for End-Stage Liver Disease – Sodium). Patients with persistent elevation of the CLIF-SIG score had the highest mortality risk.

Validation in external cohorts (including non-cirrhotic patients with sepsis or septic shock) confirmed the relevance of the 28-gene panel. Key contributors include genes involved in inflammasome activation (e.g., PYCARD (Apoptosis-associated speck-like protein containing a CARD)), macrophage activity (CD163 (Cluster of Differentiation 163)), and NK (natural killer) cell function (e.g., GZMH (Granzyme H), XCL1 (Chemokine (C motif) ligand 1)), aligning with known SI mechanisms in liver failure.

The CLIF-SIG score provides a more precise quantification of SI in ADC than current biomarkers. It has potential to improve patient stratification, guide immunomodulatory therapy, and monitor response longitudinally. While not yet ready for bedside use, development of rapid clinical assays is underway.