Fibroblast activation assessed by PRO-C3 and PRO-C6 is associated to accumulation of key bile acids - A hallmark of fibrosis initiation and mortality in alcohol-related liver disease

EASL CONGRESS 7-10 May 2025 Amsterdam, the Netherlands

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BACKGROUND

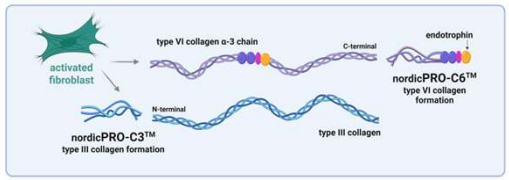
- Alcohol-related liver disease (ALD) results from persistent liver damage due to excessive alcohol consumption [1].
- ALD promotes the disruption of bile acid homeostasis, further contributing for the development of liver fibrosis and disease progression to cirrhosis, and end-stage liver failure [2].
- The use of anti-fibrotic therapy has shown to simultaneously reduce bile accumulation and levels of fibroblast activity biomarker PRO-C3. However, the role of bile acids as drivers of fibrogenesis remains unclear [3].

The present work aims to investigate the link between bile accumulation in ALD and fibrosis induction ALD by exploring associations between fibroblast activity biomarkers, bile acids, and clinical outcomes.

METHODS

- GALAXY GALA-ALD study: cross-sectional cohort of 450 patients with biopsy-proven ALD.

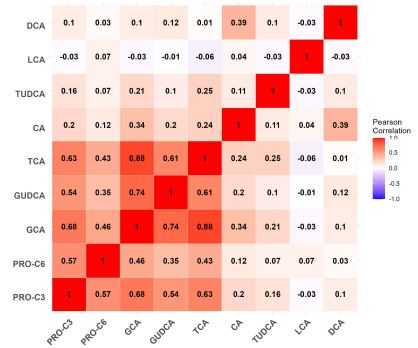
- Serum levels of nordicPRO-C3™ and nordicPRO-C6™ were obtained by ELISA; and plasma concentrations of bile acids (CA, TCA, GCA, LCA, DCA, TUDCA, GUDCA) were obtained by liquid chromatography/mass-spectrometry (UHPLC-MS).



RESULTS

Fibroblast activation correlates to bile acids

Figure 1. Spearman's correlation matrix and coefficients between bile acids and fibroblast activation biomarkers PRO-C3 and PRO-C6 at baseline.



- Strong correlations between fibroblast activation markers PRO-C3 and PRO-C6 and glycine conjugated bile acids GCA (r=0.67 for PRO-C3 and r= 0.45 for PRO-C6) and GUDCA (r= 0.53 for PRO-C3 and r=0.34 for PRO-C6); taurine conjugated bile acid TCA (r=0.64 for PRO-C3 and r=0.46 for PRO-C6) at baseline.

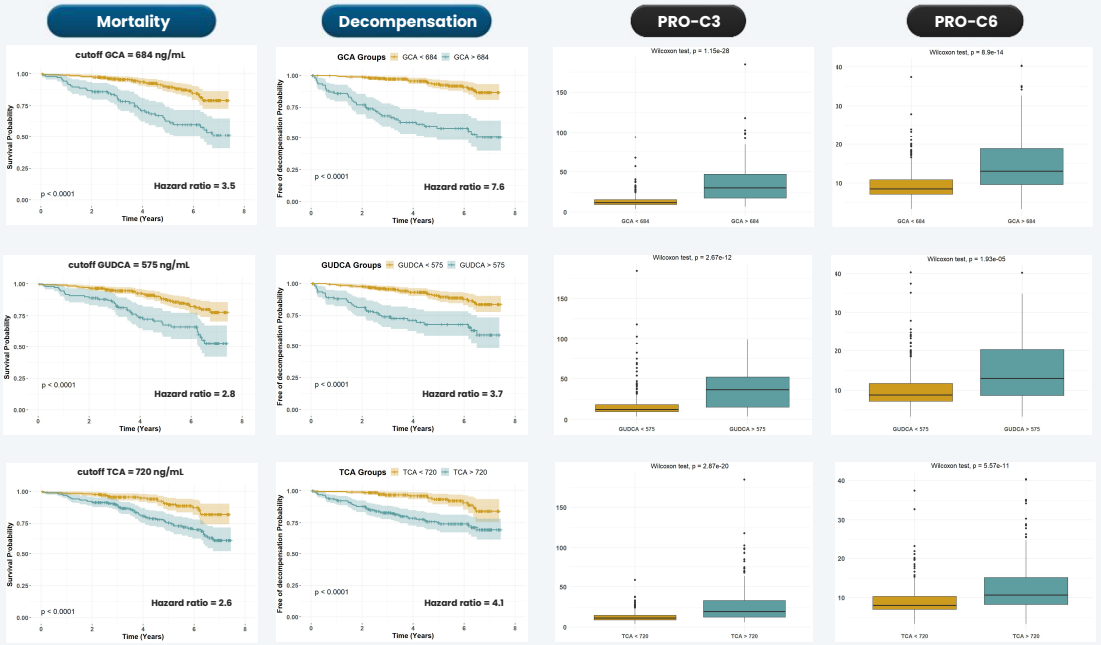
CONCLUSIONS

- **Increased circulating levels of toxic bile acids are associated to fibroblast activation and poor prognosis in ALD.**
- **The data suggests that bile acids are linked to activation of fibrogenesis and, therefore, may induce the development of liver fibrosis in ALD.**

ALD patients with increased risk of mortality and decompensation have higher levels of bile acids and fibroblast activity markers PRO-C3 and PRO-C6

Figure 2. Kaplan-Meier curves stratifying ALD patients at risk of mortality and decompensation according to bile acid thresholds (GCA_{cutoff} = 684 ng/mL; TCA_{cutoff} = 720 ng/mL ; $GUDCA_{cutoff}$ = 575 ng/mL) previously determined as the upper quartile (Q4).

Figure 3: ALD patients with higher baseline levels of GCA (> 684 ng/mL); TCA (> 720 ng/mL) and GUDCA (> 575 ng/mL) and higher risk of mortality and decompensation also exhibited significantly higher levels of fibroblast activity markers PRO-C3 and PRO-C6 at baseline.



Fibroblast activation in ALD patients is associated with disrupted bile acid homeostasis and increased risk of outcomes

REFERENCES
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ACKOWLEDGEMENTS and FUNDING
European Union's Horizon 2020 research and innovation programme under grant agreement number 668031

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