Hot & cold fibrosis: fibro-inflammatory biomarkers as prognostic tools in alcohol-related liver disease

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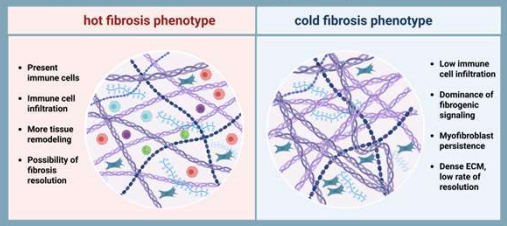
BACKGROUND

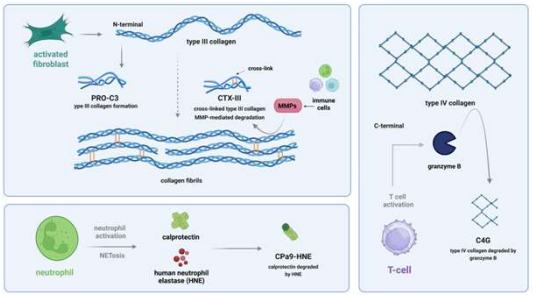
- Alcohol overuse can trigger liver inflammation, which may progress to fibrosis and cirrhosis—stages within the spectrum of alcohol-related liver disease (ALD) [1].
- The combination of fibrotic and inflammatory processes drives the course of ALD progression and influences the risk of clinical outcomes[2].
- The new concept of "hot & cold fibrosis" - defined by the presence (hot) or absence (cold) of immune cells within fibrotic tissues – can help to understand the degree of inflammation associated with liver fibrosis and its impact in ALD progression[2].



This study aims to investigate how immune cell activity biomarkers can improve the prognostic performance of fibrogenesis biomarkers with established prognostic value for risk stratification in ALD.

METHODS

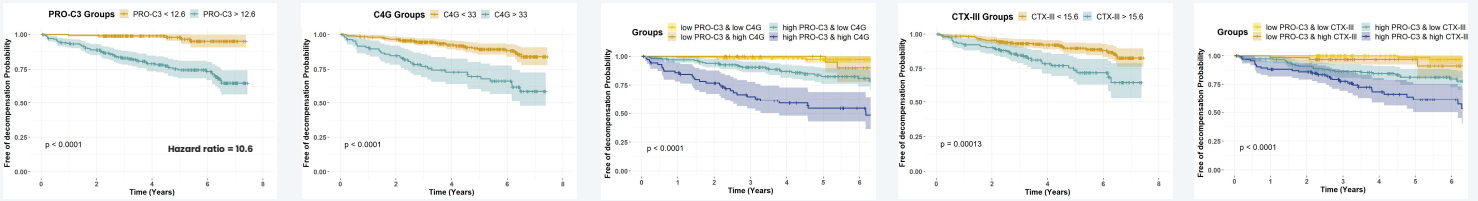
- GALAXY GALA-ALD study: cross-sectional cohort of 450 patients with biopsy-proven ALD and 147 matched healthy controls. ALD patients were followed up over 6 years.
- Hot & cold fibrosis biomarkers nordicPRO-C3™ , CTX-III, C4G and C-Pa9-HNE were measured in serum from GALA-ALD study.



RESULTS – Prognostic value of biomarkers

Figure 1. *Kaplan-Meier curves stratifying ALD patients at risk of decompensation and all-cause mortality according to thresholds of PRO-C3 (PRO-C3$_{cutoff}$ = 12.6 ng/mL; from literature; C4G (C4G$_{cutoff}$ = 33 ng/mL ; cutoff determined as the upper quartile (Q4); CTX-III (CTX-III$_{cutoff}$ = 15.6 ng/mL; determined as the upper quartile (Q4)).*

Decompensation



Mortality

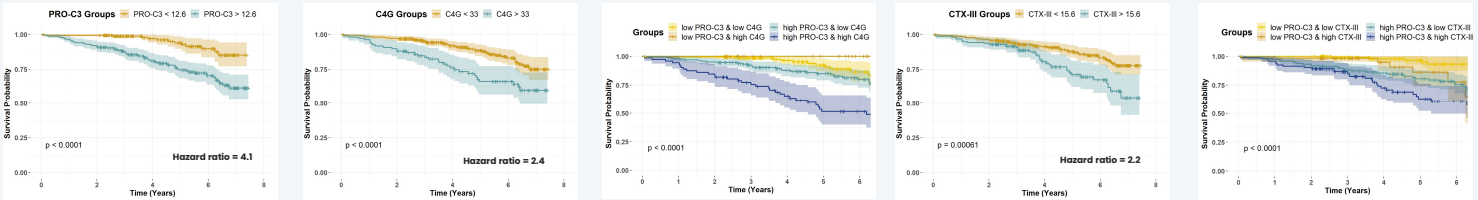


Table 1. *Hazard ratios for ALD patient groups stratified according to biomarker cutoffs based on the risk of decompensation.*

Groups	Hazard_Ratio [95% CI]
Low PRO-C3 & low C4G	1.00
Low PRO-C3 & high C4G	4.12 [0.69 – 24.68]
high PRO-C3 & low C4G	12.06 [2.84 – 5.16]
high PRO-C3 & high C4G	31.67 [7.63 – 131.49]

Groups	Hazard_Ratio [95% CI]
Low PRO-C3 & low CTX-III	1.00
Low PRO-C3 & high CTX-III	2.94 [0.33 – 26.28]
high PRO-C3 & low CTX-III	13.38[1.74 – 102.93]
high PRO-C3 & high CTX-III	26.94 [3.72 – 195.20]

Table 2. *Hazard ratios for ALD patient groups stratified according to biomarker cutoffs based on the risk of all-cause mortality.*

Groups	Hazard_Ratio [95% CI]
Low PRO-C3 & low C4G	1.00
Low PRO-C3 & high C4G	No events
high PRO-C3 & low C4G	2.61 [1.34 – 5.11]
high PRO-C3 & high C4G	7.32 [3.77 – 14.23]

Groups	Hazard_Ratio [95% CI]
Low PRO-C3 & low CTX-III	1.00
Low PRO-C3 & high CTX-III	2.94 [0.33 – 26.28]
high PRO-C3 & low CTX-III	13.38[1.74 – 102.93]
high PRO-C3 & high CTX-III	26.94 [3.72 – 195.20]

Combined biomarkers improve prognostic value for stratification of patients at risk of outcomes

CONCLUSIONS

- **ALD patients at higher risk of clinical outcomes are characterized by increased fibrogenesis and increased inflammation.**
- **Combining biomarkers reflecting different biological processes improved the prognostic performance of individual biomarkers and may aid in selecting personalized treatment based on distinct patient profiles.**

REFERENCES
[1] Thiele et al., 2021. Aliment Pharmacol Ther vol 54 (8).
[2] Zawadzki et al, 2025. JHEP.

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