Early alcohol relapse after an episode of alcohol‐induced hepatitis (AH): prevalence, impact on liver function, genetic and non‐genetic factors and identification of distinct risk profiles.

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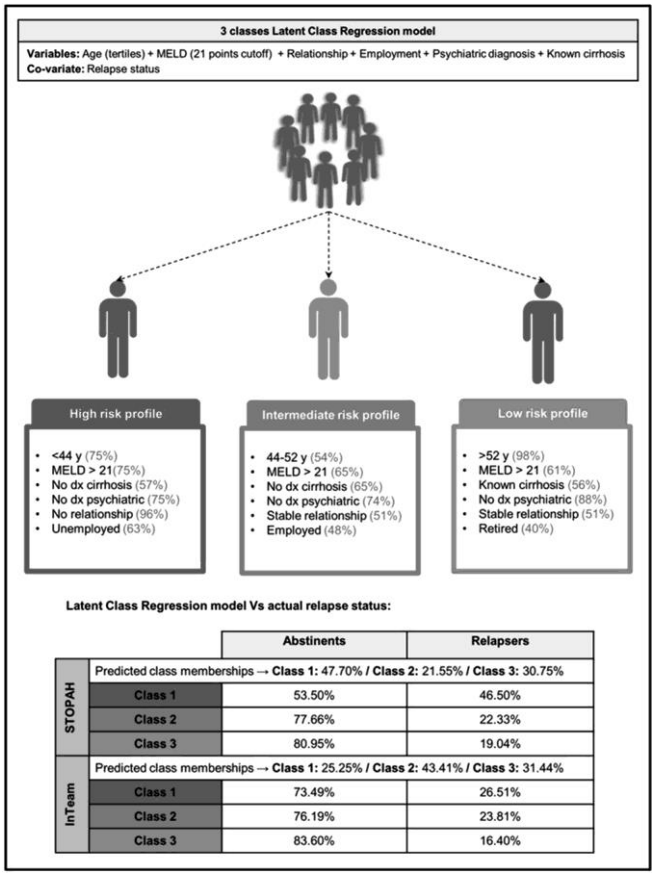
Background: Alcohol relapse negatively influences long-term survival in AH. No studies have identified the prevalence and predictors of early relapse. We aimed to determine its prevalence within 3 months of presentation with AH, its impact on liver function, and genetic and non-genetic predictors in order to develop a tool to estimate relapse risk.**Methods:** Demographic, biochemical and genetic data with 90 day drinking status were obtained from 478 patients of STOPAH trial. Ten single nucleotide polymorphisms (SNPs) recently associated with Problematic Alcohol Use (PAU; Zhou H et al Nat Neurosci. 2020) and a polygenic risk score from 2,000 SNPs were also evaluated. Logistic regression (LR) was used to test associations with relapse and Latent Class Regression (LCR) to identify latent profiles with different relapse risk. Results were validated in a cohort of 194 patients from InTeam Consortium. **Results:** Three-month relapse was 33% and 22% in the STOPAH and InTeam cohorts, respectively. Relapse impaired improvement in liver function at 90 days compared to abstinence in a dose-dependent fashion. Age [OR 0.97 (0.94 - 0.99) p=0.02)], former smoking [OR 0.51 (0.27 - 0.93) p=0.03)], long-term sickness [OR 1.90 (1.00 – 3.64) p=0.04)], MELD [OR 0.91 (0.85 - 0.97) p=0.005)] and stable relationship [OR 1.97 (1.20 – 3.29) p=0.008)] were independent predictors in multivariate analysis. A single SNP (rs62250713) was borderline significant. MELD [OR 0.89 (0.82 - 0.96) p=0.004)] and social support [OR 3.68 (1.65 – 8.41) p=0.001)] were independent predictors in InTeam cohort. The variables significant in LR and available in both datasets were used for LCR. Three latent profiles were identified: High risk patients who were mostly younger, unemployed and had no stable relationship; intermediate risk, composed of middle aged patients in employment and a stable relationship; and low risk profile of older patients most likely with known cirrhosis, retired and in a stable relationship. The actual prevalence of relapse in each class was 46.50%, 22.33% and 19.04% in STOPAH and 26.51%, 23.81% and 16.40% in InTeam cohort respectively (Fig.1). **Conclusion:** Early relapse after an AH episode is a frequent event with a significant dose-dependent impact on liver function. Non-genetic factors

predict early relapse whilst targeted loci associated with PAU seems not to significantly alter the risk in this cohort. LCR can identify distinct profiles with differing relapse risk that may permit personalisation of treatment strategies.



Latent Class Regression model Vs actual relapse status:

		Abstinents	Relapsers
STOPAH	Predicted class memberships → **Class 1:** 47.70% **/ Class 2:** 21.55% **/ Class 3:** 30.75%		
	Class 1	53.50%	46.50%
	Class 2	77.66%	22.33%
	Class 3	80.95%	19.04%
InTeam	Predicted class memberships → **Class 1:** 25.25% **/ Class 2:** 43.41% **/ Class 3:** 31.44%		
	Class 1	73.49%	26.51%
	Class 2	76.19%	23.81%
	Class 3	83.60%	16.40%