Predicting significant hepatic steatosis from routine biochemistry in people with and without type 2 diabetes (T2D)

Magdalena Nowak¹, Andrea Dennis¹, Helena Thomaides Brears¹, Rajarshi Banerjee¹, Kenneth Cusi², Naim Alkhouri³, Daniel Cuthbertson⁴

¹Perspectum Ltd., Oxford, United Kingdom, ²University of Florida, Gainesville, FL, United States, ³Arizona Liver Health, Chandler, Arizona, United States, ⁴University of Liverpool, Liverpool, United Kingdom

Background and Aims: Quantifying liver fat content (LFC) using MRI and assessing LFC change in response to therapy has been widely used as a primary endpoint in early-phase clinical trials of therapeutic agents for metabolic dysfunction-associated liver disease (MASLD). Identifying individuals with LFC of 8% or higher is typically used as an inclusion criterion and various blood-based biomarkers have been proposed, but their value has not been extensively studied in T2D. We aimed to identify the optimal combination of anthropometric and routinely available biochemical tests to better identify patients with high LFC.

Method: Data from participants with suspected MASLD were pooled from three clinical studies; with T2D (N=173, 41% female, median age: 60y, mean: LFC=11%, BMI 31kg/m²) and without T2D (N=114, 46% female, median age: 55y, mean: LFC=12%, BMI 31kg/m²). Additional validation datasets were analysed: with T2D (N=305, 43% female, median age: 58y, mean: LFC=16%, BMI 34kg/m²) and without (N=452, 51% female, median age: 49y, mean: LFC=10%, BMI 30kg/m²). LFC was measured using either magnetic resonance imaging (proton-density fat fraction) or proton magnetic resonance spectroscopy. The diagnostic accuracy was evaluated using Area Under the Receiver Operating Characteristic curve (AUROC). Stepwise logistic regression was performed to select the optimal combination of continuous predictor variables. The Fatty Liver Index (FLI), Hepatic Steatosis Index (HSI) and controlled attenuation parameter (CAP) measured by Fibroscan were also assessed, where available.

Results: LFC (≥ 8%) was most effectively predicted by a simple combination of serum ALT and triglycerides. This model showed good diagnostic accuracy, in both training and validation datasets, in individuals with T2D (Training: AUC 0.78, CI: 0.68-0.88; PPV=0.86; Validation: AUC: 0.83, CI: 0.78-0.88, PPV=0.88) and without (Training: AUC: 0.83, CI: 0.73-0.93; PPV=0.88; Validation: AUC: 0.86, CI: 0.82-0.90, PPV=0.7). Addition of waist circumference did not significantly increase AUC (0.82-0.87; DeLong test p>0.05). The accuracy of FLI and HSI was less consistent across both T2D and non-T2D groups (FLI, AUC range: 0.73-0.82, PPV range=0.53-0.9; HSI, AUC range: 0.72-0.76, PPV range=0.57-0.86). In T2D, the CAP score was less accurate (AUC: 0.71, CI: 0.58-0.83; PPV=0.77).

Conclusion: This study demonstrates that the combination of ALT and triglycerides accurately identifies patients with LFC of 8% or higher. The integration of such models into the patient recruitment process in hepatology and endocrinology clinics could effectively reduce screen failure rates in clinical trials for MASLD.