Unveiling determinants of nonalcoholic fatty liver disease (NAFLD) activity and nonalcoholic steatohepatitis (NASH) using item response modeling

THU-033

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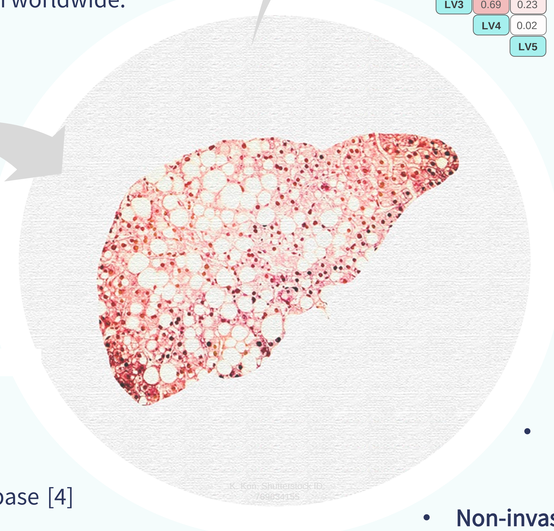
Introduction

- **NAFLD** and its **progressive subtype NASH** have emerged as a leading indication for liver transplantation and, fueled by the obesity epidemic, as an **alarmingly increasing** threat to public health worldwide.
- To date, there are **no approved drug therapies** for NAFLD/NASH. Drug development has been challenged by the complex, 'multi-hit' pathophysiology of NAFLD, inconsistent diagnostic criteria and lack of clarity about treatment endpoints [1,2].
- NASH **diagnosis and clinical trial endpoints** heavily rely on **liver biopsies** and histological scores, e.g. the NAFLD activity score (NAS; Fig. 3a) or the fibrosis stage [3].
- Our **objective** was to **enhance the understanding** of **disease processes** underlying NAFLD and to assess the role of different histological and **non-invasive markers** in assessing NAFLD severity by using item response theory (IRT) modeling.



Methods

- The **study population** (n_{ID}=914) originated from the public NIDDK NAFLD Adult Database [4] and spanned the full spectrum of NAFLD (NAS 0-8: Fig. 1; 52.3% with NASH).
- We developed an **IRT model** (using R3.6.1/mirt [5]), relating the probability of the outcome of each item (i.e. histological score) to latent variables (LV), which represent 'hidden' disease processes underlying the item responses (Fig. 3a).
- **Covariates** predicting NAFLD activity were identified using full random effects modeling (FREM, PsN 4.10.0 [6]), followed by a bootstrap (n=100 samples).

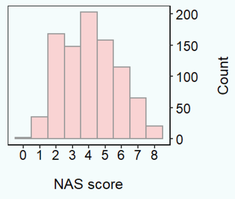


Figure 1. Distribution of the NAS score in the population (n=914)

- Diverse **types of covariates** were screened (Fig. 2). Covariates were selected for final FREM (Fig. 4) if the mean expected scores corresponding to their 2.5th and 97.5th percentile spanned ≥25% of the NAS or fibrosis score.

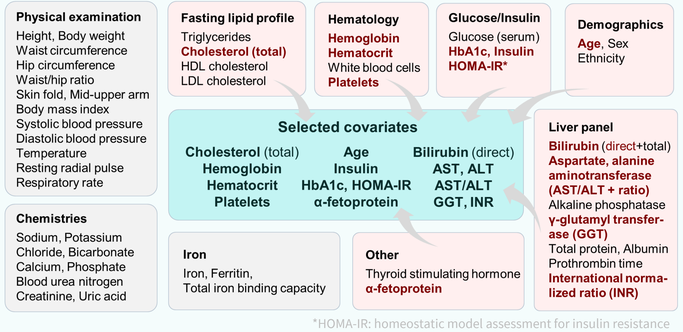


Figure 2. Investigated covariates (grey+red shaded) as non-invasive biomarkers for NAFLD; green: covariates selected for final FREM

Results

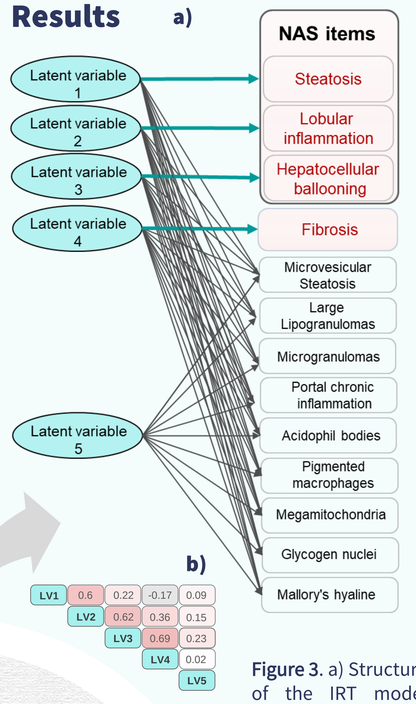


Figure 3. a) Structure of the IRT model based on 13 diverse histological lesions (5 graded, 8 binary scores); b) Correlation between latent variables (LV)

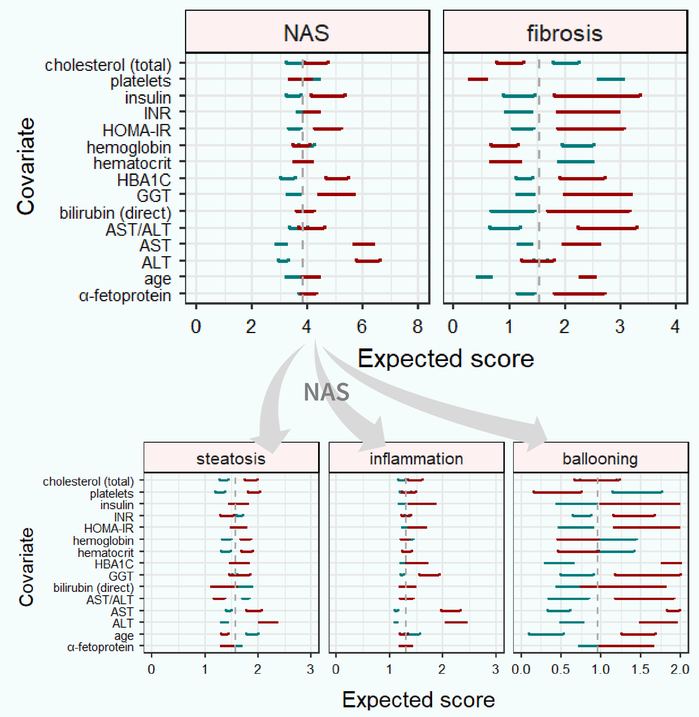


Figure 4. Impact of selected covariates on the expected NAS and fibrosis score. Green/red bars represent expected scores and associated uncertainty given the 2.5th/97.5th percentile of the covariate; vertical dashed lines depict mean scores.

- The IRT model (Fig. 3a) suggested **different disease processes** (i.e. separate latent variables LV) for the **4 cardinal features of NAFLD**, i.e. 1 LV each for the 3 NAS items and fibrosis and 1 LV covering merely residual items. One LV resulted insufficient to adequately describe the NAS items, also in a sparse 3-item (NAS) model.
- **Highest correlation** (70%) was found between disease processes reflected by **hepatocellular ballooning and fibrosis** (i.e. latent variables 3 and 4; Fig. 3b).
- **Non-invasive biomarkers best reflecting NAFLD severity** (Fig. 2 and 4) included the liver enzymes AST and ALT (→ NAS score) as well as platelets and age (→ fibrosis score). Of the 3 NAS components, hepatocellular ballooning resulted to be most sensitive to changes of the covariates.

- An **item response theory model** based on **histological liver scores** allowed to jointly characterize disparate **disease processes underlying NAFLD,** including more rapidly (steatosis) and slowly (fibrosis) changing lesions.
- Different **non-invasive biomarkers** were markedly correlated with **different biopsy features**, e.g. the liver enzymes AST and ALT with the NAS score and platelets and age with the fibrosis stage.

Perspectives

- The model lays the basis for **future investigations**, e.g. on the **sensitivity of the NAS** to changes of different disease processes (e.g. as response to a therapeutic intervention)—with the ultimate goal to support **model-informed drug development**.

References

[1] Wong et al. Lancet Gastroenterol Hepatol. 2016; 1:56–67. [2] Rinella et al. J Hepatol. 2019; 71:823–833. [3] Kleiner et al. Hepatology. 41:1313–1321. [4] Neuschwander-Tetri et al. Hepatology. 2010; 52:913–924. [5] Chalmers. J Stat Softw. 2012; 48:1-29. [6] https://uupharmacometrics.github.io/PsN