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Serum metabolomics-based steatohepatitis score for the non-invasive identification of patients with non-alcoholic steatohepatitis (NASH) in multiethnic, including type 2 diabetes mellitus population

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1 Introduction and Aim

The prevalence of nonalcoholic fatty liver disease (NAFLD) is high in the western world and it is often comorbid with type 2 diabetes mellitus (T2DM).

We aimed to develop an accurate, serum-based, easy to use test independent of glycated hemoglobin (HbA1c) for the diagnosis of nonalcoholic steatohepatitis (NASH) regardless of the presence of T2DM.

2 Method

Serum metabolomic testing was performed in an original cohort of 682 patients that was subsequently blind validated in two separate international cohorts of 202 patients (100 from Chile and 102 from USA). The derivation cohort was a cross-sectional, multicenter study of patients aged 18 years or older, who underwent liver biopsy for suspicion of NAFLD. To classify those patients with NASH, a NAFLD Activity Score (NAS) ≥3 (with at least one point on each of steatosis, lobular inflammation and ballooning) was considered. The best fitting multivariable logistic regression model was identified and internally validated using a K-fold Cross-Validation process. Score calibration and discrimination performance were determined in both the derivation and validation datasets.

3 Results

We performed serum metabolomic testing in a multiethnic, multicenter derivation cohort of 682 subjects with biopsy proven NAFLD (312 Steatosis, 370 NASH). The characteristics of this cohort were 51% Male, BMI 35.5 ± 7.3 kg/m^2; alanine aminotransferase, ALT 51.4 ± 37.6 U/L; aspartate aminotransferase, AST 37.2 ± 24.3 U/L and HbA1c 6.5 ± 1.2 %.

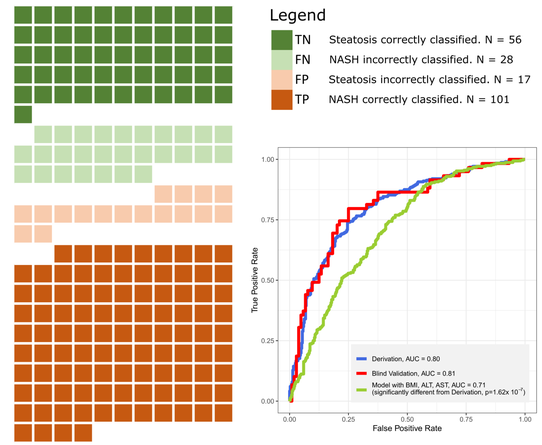
The final score (OWLiverDM2) includes 16 lipids, BMI, AST and ALT. Using logistic regression analysis, we could discriminate between patients with NASH and steatosis. The diagnostic performance of the OWLiverDM2 showed an area under the receiver operating characteristic curve (AUC) of 0.80 ± 0.03, while a model generated with only clinical variables, could only reach to an AUC of 0.71 ± 0.04.

Furthermore, the new test maintained a better performance and the statistical significance versus the clinical algorithm in a subgroup of 406 subjects with T2DM or HbA1c >= 6 %, AUC= 0.78 versus AUC= 0.71 (Delong test, z-score = 3.064, p-value = 0.00218).

4 Results

Finally, we validated OWLiverDM2 performance in an independent cohort of 202 patients of similar characteristics, obtaining an AUC of 0.81 ± 0.02

Figure 1. *OWLiver DM2 Score performance in validation cohort.*



Each square represents a patient in the validation cohort. Dark colors mean correctly classified patients and light colors missed classified. Table 1 shows the metrics for the model in both the derivation and validation cohorts

Table 1. *OWLiver DM2 Score performance. Area under de curve (AUC), Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for* derivation *and validation cohorts.*

ROC Analysis					
Cohort	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Derivation	0.80	0.74	0.73	0.71	0.77
Validation	0.81	0.78	0.76	0.66	0.85

5 Conclusions

The new serum-based OWLiverDM2 score accurately discriminates between steatosis and NASH in a more general, multiethnic, including controlled and non-controlled T2DM population without using HbA1c.

6 References

1. Barr J et al. Obesity-dependent metabolic signatures associated with nonalcoholic fatty liver disease progression. J Proteome Res. 2012;11(4):2521-32.
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7 Contact information

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